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(57) Abstract

This invention relates to compounds which inhibit cathepsin K and are useful for treating diseases of excessive bone or cartilage loss.

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INHIBITORS OF CYSTEINE PROTEASE

FIELD OF THE INVENTION

This invention relates to compounds which inhibit cathepsin K and are useful for treating diseases of excessive bone or cartilage loss, e.g., osteoporosis, periodontitis and arthritis.

BACKGROUND OF THE INVENTION

Bone is composed of a protein matrix in which spindle- or plate-shaped crystals of hydroxyapatite are incorporated. Type I Collagen represents the major structural protein of bone comprising approximately 90% of the structural protein. The remaining 10% of matrix is composed of a number of non-collagenous proteins, including osteocalcin, proteoglycans, osteopontin, osteonectin, thrombospondin, fibronectin, and bone sialoprotein. Skeletal bone undergoes remodeling at discrete foci throughout life. These foci, or remodeling units, undergo a cycle consisting of a bone resorption phase followed by a phase of bone replacement.

Bone resorption is carried out by osteoclasts, which are multinuclear cells of hematopoietic lineage. The osteoclasts adhere to the bone surface and form a tight sealing zone, followed by extensive membrane ruffling on their apical (i.e., resorbing) surface. This creates an enclosed extracellular compartment on the bone surface that is acidified by proton pumps in the ruffled membrane, and into which the osteoclast secretes proteolytic enzymes. The low pH of the compartment dissolves hydroxyapatite crystals at the bone surface, while the proteolytic enzymes digest the protein matrix. In this way, a resorption lacuna, or pit, is formed. At the end of this phase of the cycle, osteoblasts lay down a new protein matrix that is subsequently mineralized. In several disease states, such as osteoporosis and Paget's disease, the normal balance between bone resorption and formation is disrupted, and there is a net loss of bone at each cycle. Ultimately, this leads to weakening of the bone and may result in increased fracture risk with minimal trauma.

Several published studies have demonstrated that inhibitors of cysteine proteases are effective at inhibiting osteoclast-mediated bone resorption, and indicate an essential role for a cysteine proteases in bone resorption. For example, Delaisse, *et al.*, *Biochem. J.*, **1980**, *192*, 365, disclose a series of protease inhibitors in a mouse bone organ culture system and suggest that inhibitors of cysteine proteases (e.g., leupeptin, Z-Phe-Ala-CHN_2) prevent bone resorption, while serine protease inhibitors were ineffective. Delaisse, *et al.*, *Biochem. Biophys. Res. Commun.*, **1984**, *125*, 441, disclose that E-64 and leupeptin are also effective at preventing bone resorption *in vivo*, as measured by acute changes in serum calcium in rats on calcium deficient diets. Lerner, *et al.*, *J. Bone Min. Res.*, **1992**, *7*, 433, disclose that cystatin, an endogenous cysteine protease inhibitor, inhibits PTH stimulated bone resorption in mouse calvariae. Other studies, such as by Delaisse, *et al.*, *Bone*, **1987**, *8*, 305, Hill, *et al.*, *J. Cell. Biochem.*, **1994**, *56*, 118, and Everts, *et al.*, *J. Cell. Physiol.*, **1992**, *150*, 221, also report a correlation between inhibition of cysteine protease activity

and bone resorption. Tezuka, *et al.*, *J. Biol. Chem.*, **1994**, *269*, 1106, Inaoka, *et al.*, *Biochem. Biophys. Res. Commun.*, **1995**, *206*, 89 and Shi, *et al.*, *FEBS Lett.*, **1995**, *357*, 129 disclose that under normal conditions cathepsin K (which has also been called cathepsin O and cathepsin O2), a cysteine protease, is abundantly expressed in osteoclasts and may be the major cysteine protease present in these cells.

The abundant selective expression of cathepsin K in osteoclasts strongly suggests that this enzyme is essential for bone resorption. Thus, selective inhibition of cathepsin K may provide an effective treatment for diseases of excessive bone loss, including, but not limited to, osteoporosis, periodontitis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease. Cathepsin K levels have also been demonstrated to be elevated in chondroclasts of osteoarthritic synovium. Thus, selective inhibition of cathepsin K may also be useful for treating diseases of excessive cartilage or matrix degradation, including, but not limited to, osteoarthritis and rheumatoid arthritis. Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix. Thus, selective inhibition of cathepsin K may also be useful for treating certain neoplastic diseases.

Palmer, *et al.*, *J. Med. Chem.*, **1995**, *38*, 3193, disclose certain vinyl sulfones which irreversibly inhibit cysteine proteases, such as the cathepsins B, L, S, O2 and cruzain. Other classes of compounds, such as aldehydes, nitriles, a-ketocarbonyl compounds, halomethyl ketones, diazomethyl ketones, (acyloxy)methyl ketones, ketomethylsulfonium salts and epoxy succinyl compounds have also been reported to inhibit cysteine proteases..

International Patent Application No. PCT/US93/07767, and European Patent Application Nos. EP 0 525 420 A1, EP 0 603 873 A1, and EP 0 611 756 A2 describe alkoxymethyl and mercaptomethyl ketones which inhibit the following cysteine proteases: cathepsins B, H and L. International Patent Application No. PCT/US94/08868 and and European Patent Application No. EP 0 623 592 A1 describe alkoxymethyl and mercaptomethyl ketones which inhibit the cysteine protease IL-1b convertase. Alkoxymethyl and mercaptomethyl ketones have also been described as inhibitors of the serine protease kininogenase (International Patent Application No. PCT/GB91/01479).

We have now discovered a novel class of alkoxymethyl ketone inhibitors of cysteine proteases, particularly cathepsin K.

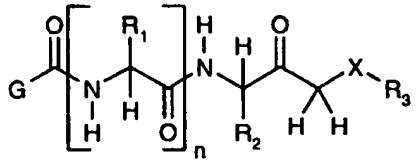
SUMMARY OF THE INVENTION

An object of the present invention is to provide compounds which inhibit cysteine proteases, particularly cathepsin K, and which are useful for treating diseases which may be therapeutically modified by altering the activity of such proteases. Accordingly, in the first aspect this invention provides a compound according to Formula I. In another aspect, this invention provides a pharmaceutical composition comprising a compound according to Formula I and a pharmaceutically acceptable carrier, diluent or excipient. In yet another aspect, this invention provides a method of treating diseases in which the disease pathology may be therapeutically modified by inhibiting cysteine protease, especially cathepsin K. In

a particular aspect, the compounds of this invention are useful for treating diseases characterized by bone loss, such as osteoporosis and periodontitis or by excessive cartilage or matrix degradation, such as osteoarthritis.

DETAILED DESCRIPTION

The present invention provides compounds of Formula I:



I

G = $ArCHR^4O$, C_{1-4}alkyl, CH_2OAr, Ar, OCH_2C_{3-6}cycloalkyl, CH_2-imidazole, $ArSO_2$, NR^5CH_2Ar, NCH_2Ar, NAr, where the ortho position of Ar may be connected to the nitrogen by a 2 or 3 carbon chain to form a 6-membered ring;

R^1 = C_{4-6}alkyl, CH_2Ar, CH_2-C_{3-6}cycloalkyl;
with the proviso that when R^1 = isobutyl, the stereochemistry at the adjacent center is of the (S)-configuration;

R^2 = H, methyl, C_2-C_3alkyl optionally substituted by CO_2R^6 or NHR^7, isobutyl;
with the provisos that:
(a) when R^2 = isobutyl, the stereochemistry at the adjacent center must be of the (S)-configuration;
(b) when R^2 = H, methyl, R^1 cannot be CH_2Ph;

R^3 = H, C_{1-5}alkyl optionally substituted with 1-6 halogens such that no halogens are attached to the carbon adjacent to X; $(CH_2)_mAr$;

R^4 = H, C_{1-4}alkyl;

R^5 = C_{1-4}alkyl;

R^6 = H, C_{1-4}alkyl;

R^7 = H, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl;

R^8 = H, C_{1-4}alkyl;

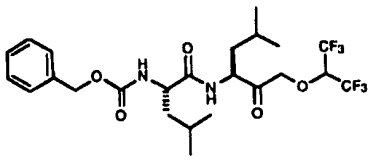
Ar = phenyl, naphthyl
optionally substituted with 1-4 substituents selected from the group consisting of: halogen; C_{1-4}alkyl; C_{1-4}alkoxy, where optionally two adjacent C_{1-4}alkoxy substituents are combined to form a methylenedioxy ring system; CO_2R^8; phenyl; and phenoxy;

n = 0, 1;

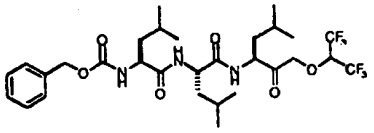
m = 0-2;

X = O, S
with the proviso that when X = S, R^3 cannot be methyl.

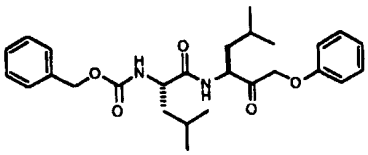
The following are preferred embodiments of the present invention:



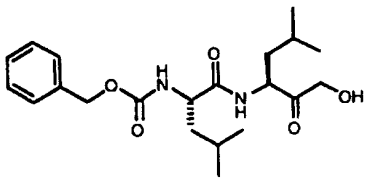
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1,1,1,3,3,3-hexafluoro-2-propoxy)-5-methyl-2-hexanone;



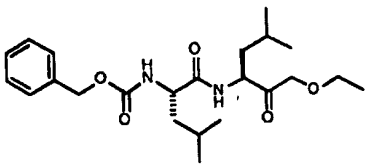
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-1-(1,1,1,3,3,3-hexafluoro-2-propoxy)-5-methyl-2-hexanone;



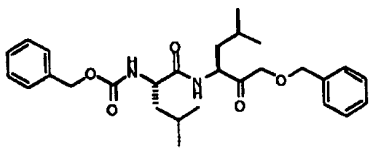
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-phenoxy-2-hexanone;



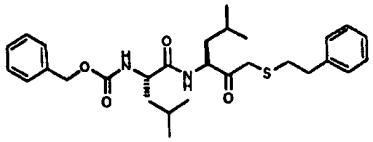
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone;



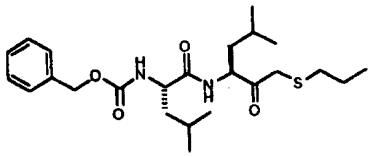
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;



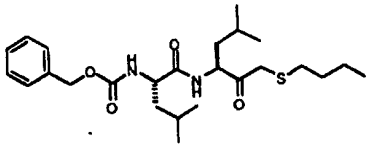
(3S)-1-benzyloxy-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-2-hexanone;



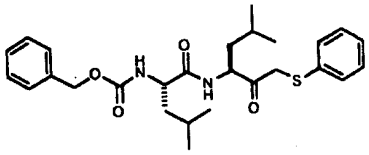
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(2-phenylethylthio)-2-hexanone;



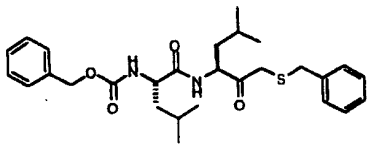
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(1-propylthio)-2-hexanone;



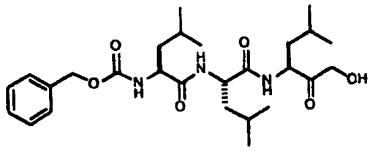
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1-butylthio)-5-methyl-2-hexanone;



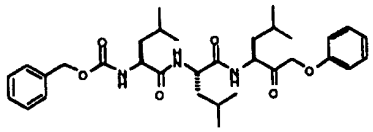
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-phenylthio-2-hexanone;



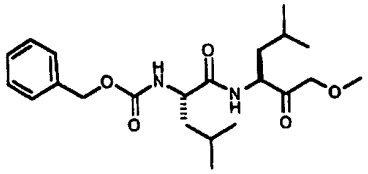
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-benzylthio-5-methyl-2-hexanone;



(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone;



(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-5-methyl-1-phenoxy-2-hexanone;



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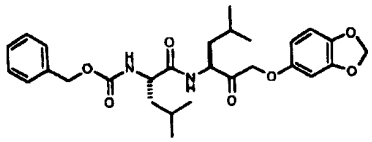
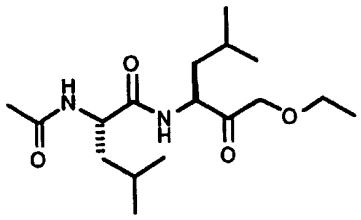
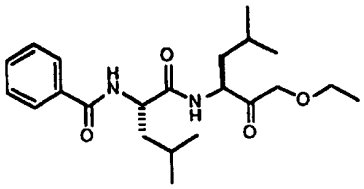


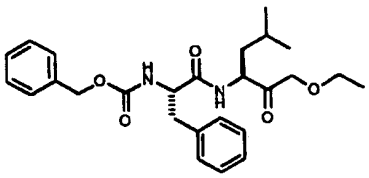
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(3,4-methylenedioxyphenoxy)-2-hexanone;



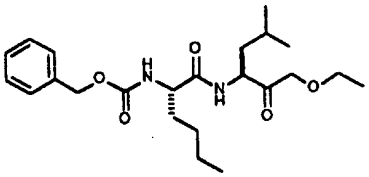
(3S)-3-[(N-acetyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;



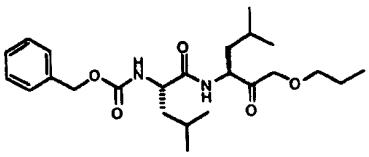
(3S)-3-[(N-benzoyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;



(3S)-3-[(N-benzyloxycarbonyl)-L-phenylalanyl]amino-1-ethoxy-5-methyl-2-hexanone;



(3S)-3-[(N-benzyloxycarbonyl)-L-norleucinyl]amino-1-ethoxy-5-methyl-2-hexanone;



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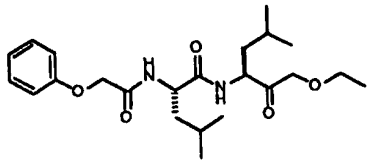

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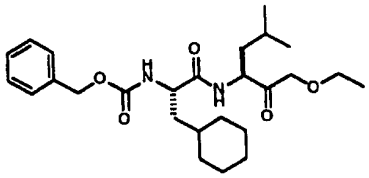

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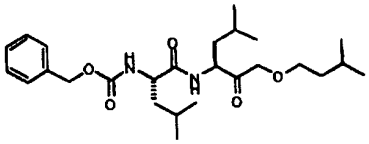

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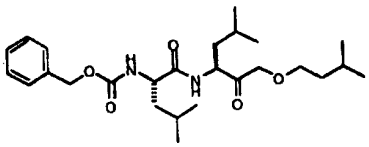

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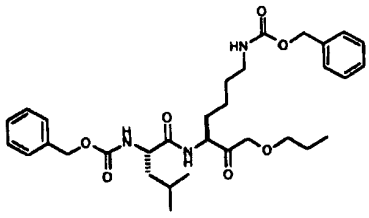
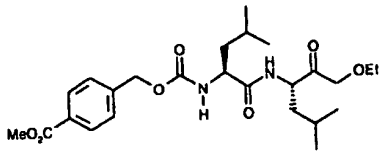
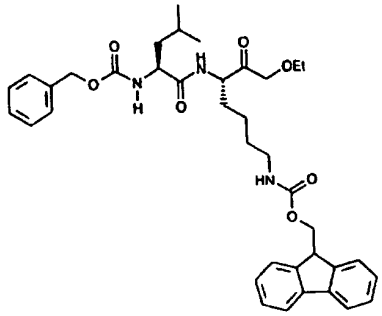


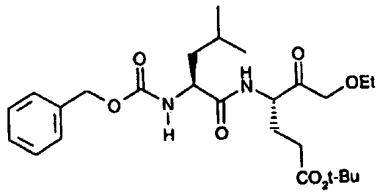
(3S)-7-[(benzyloxycarbonyl)amino]-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-2-heptanone;



(3S)-3-[[N-(4-carbomethoxy)benzyloxycarbonyl]-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;



(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-7-[(9-fluorenylmethoxycarbonyl)amino]-2-heptanone;



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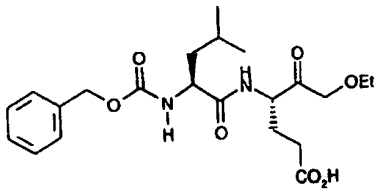
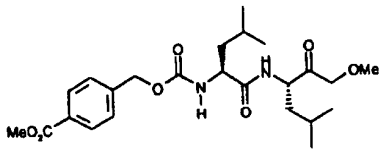
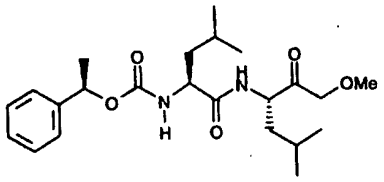


(4S)-4-[(N-benzyloxycarbonyl)-L-leucinyl]amino-6-ethoxy-5-oxohexanoic acid



(3S)-3-[[N-(4-carbomethoxy)benzyloxycarbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone;



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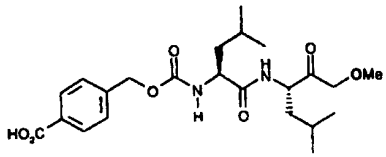

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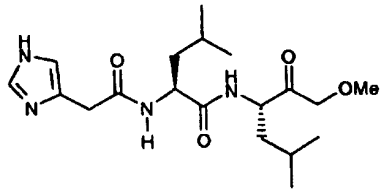

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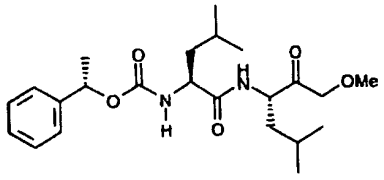

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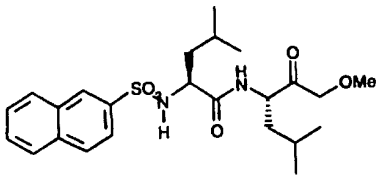
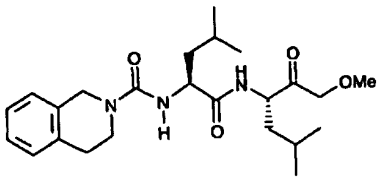
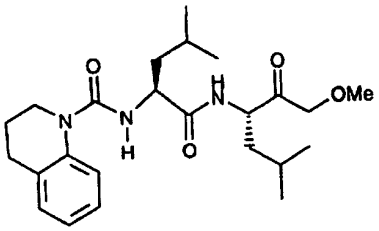


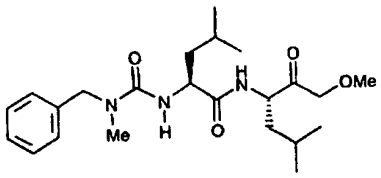
(3S)-1-ethoxy-5-methyl-3-[N-(2-naphthylsulfonyl)-L-leucinyl]amino-2-hexanone;



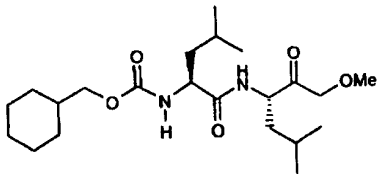
(3S)-1-ethoxy-5-methyl-3-[N-[2-(1,2,3,4-tetrahydroisoquinolyl)carbonyl]-L-leucinyl]amino-2-hexanone;



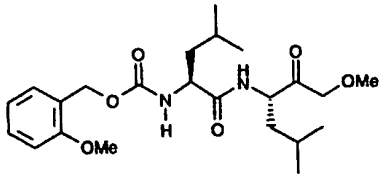
(3S)-1-ethoxy-5-methyl-3-[N-[1-(1,2,3,4-tetrahydroquinolyl)carbonyl]-L-leucinyl]amino-2-hexanone;



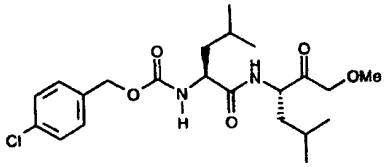
(3S)-3-[[N-(N-benzyl-N-methylamino)carbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone;



(3S)-3-[(N-cyclohexylmethoxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;



(3S)-1-methoxy-3-[[N-(2-methoxybenzyloxy)carbonyl]L-leucinyl]amino-5-methyl-2-hexanone;



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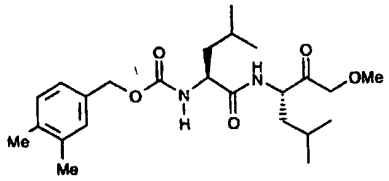

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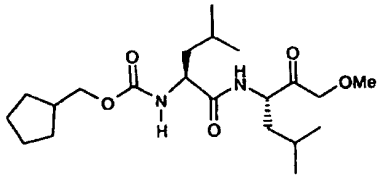
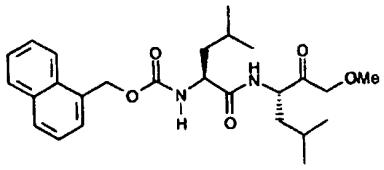
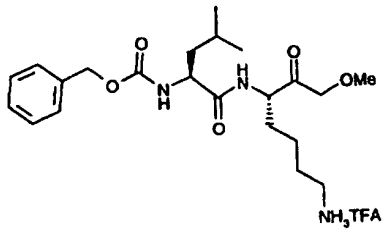


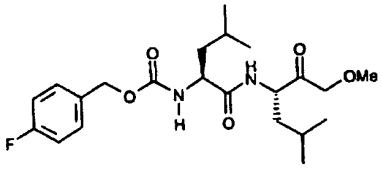
(3S)-3-[(N-cyclopentylmethoxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;



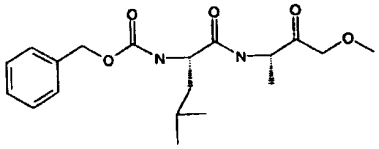
(3S)-3-[[N-(2-naphthylmethoxy)carbonyl]-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;



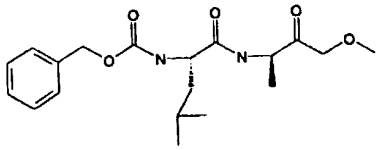
(3S)-7-amino-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-heptanone;



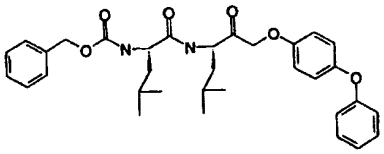
(3S)-[[N-(4-fluorobenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;



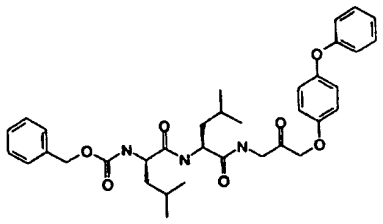
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-butanone;



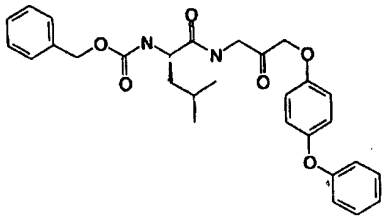
(3R)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-butanone;



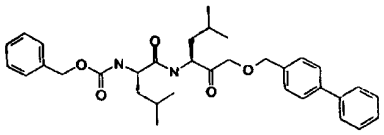
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(4-phenoxyphenoxy)-2-hexanone;



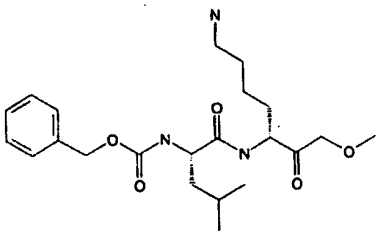
1-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanone;



1-[(N-benzyloxycarbonyl)-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanone;



(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(4-phenylbenzyloxy)-2-hexanone; and



(3R)-7-amino-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-heptanone.

Definitions

The present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds which release the active parent drug according to Formula I *in vivo*. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be

covered herein. Inventive compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases where the inventive compounds may exist in tautomeric forms, e.g., keto-enol tautomers, each tautomeric form is included within the scope of the present invention, whether existing in equilibrium or predominantly in one form.

The meaning of any substituent at any one occurrence in Formula I or any subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of the present invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984). The term amino acid as used herein refers to the D- or L- isomers of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

C_{1-6}alkyl, or any subcombination thereof, e.g. C_{1-4}alkyl, as applied herein includes, but is not limited to, as appropriate for a particular subcombination, substituted and unsubstituted methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl, pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. Any C_{1-6}alkyl group may be optionally substituted independently by one or two halogens, SR', OR', $N(R')_2$, $C(O)N(R')_2$, carbamyl or C_{1-4}alkyl, where R' is C_{1-6}alkyl.

C_{3-6}cycloalkyl includes, but is not limited to, cyclopropyl, cyclobutyl,cyclopentyl, and cyclohexyl.

Halogen means F, Cl, Br, and I.

Alkoxy means a moiety having an ether oxygen substituted with C_{1-6}alkyl, e.g., in general, -O-C_{1-6}alkyl. Optionally two adjacent C_{1-4}alkoxy substituents may be combined to form a methylenedioxy ring system. Phenoxy is -O-phenyl.

Ar, or aryl, as applied herein, means phenyl or naphthyl, or phenyl or naphthyl substituted by one to four moieties selected from the group consisting of: halogen; C_{1-4}alkyl; C_{1-4}alkoxy, where two adjacent alkoxy substituents can optionally be combined to form a methylenedioxy ring system; CO_2R^8; phenyl; and phenoxy;.

Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ar refers to the aryl radical, Ph refers to the phenyl radical, Cbz refers to the benzyloxycarbonyl radical.

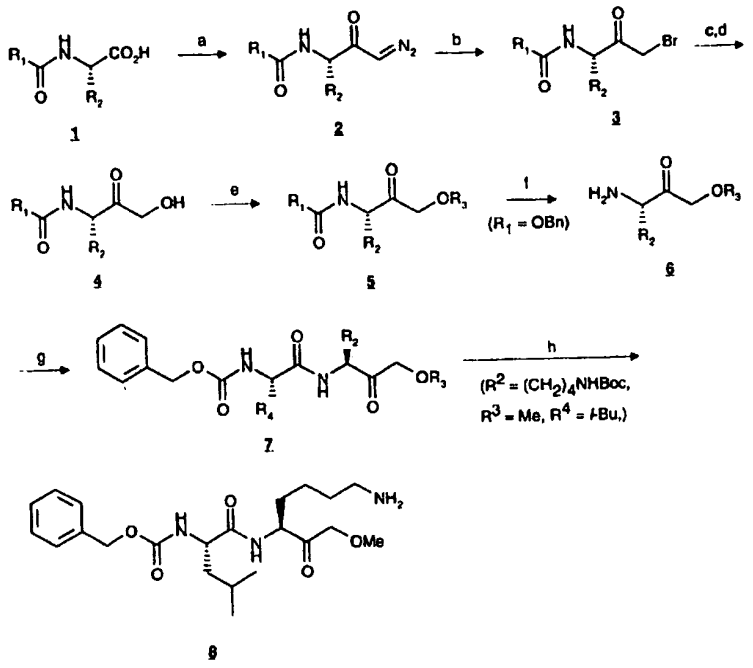
Certain reagents are abbreviated herein. DMF refers to dimethyl formamide, DEA refers to diethylamine, DIEA refers to diisopropylethylamine, EDCI refers to N-ethyl-N'(dimethylaminopropyl)-carbodiimide, HOBT refers to 1-hydroxybenzotriazole, NMM is

N-methylmorpholine, . NMP is N-methyl pyrrolidinone, TFA refers to trifluoroacetic acid, and THF refers to tetrahydrofuran.

Methods of Preparation

Compounds of the formula I wherin G = benzyloxy and X = O are prepared by methods analagous to those described in Scheme 1.

Scheme 1

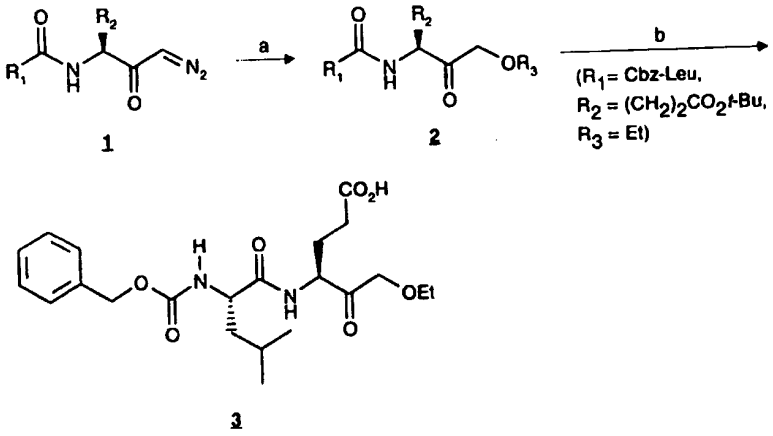


a) $ClCO_2$i-Bu, NMM, THF; CH_2N_2, Et_2O; b) Hbr, HOAc; c) $PhCOCO_2H$, KF, DMF; d) $KHCO_3$, THF; e) R^3I or R^3Br, Ag_2O, CH_2Cl_2; f) H_2, Pd/C, EtOH, 6N HCl; g) N-Cbz-amino acid, EDCI, 1-HOBT, DIEA, DMF; h) TFA, CH_2Cl_2

Diazomethyl ketone 2-Scheme 1 is prepared by activation of the N-Cbz-protected amino acid, dipeptide or tripeptide 1-Scheme 1 with isobutylchloroformate in THF followed by treatment with an ethereal solution of diazomethane. The alkoxy methyl ketone 5-Scheme 1 is prepared by formation of the bromide 3-Scheme 1 from 2-Scheme 1 with hydrogen bromide in acetic acid, displacement of the bromide with benzoyl formic acid and potassium fluoride in DMF, hydrolysis of the benzoyl formate with potassium bicarbonate in THF, and alkylation of the alcohol 4-Scheme 1 with an alkylating agent (such as ethyl iodide, methyl iodide or benzyl bromide) and silver (I) oxide in methylene chloride. Hydrogenolysis of the Cbz group with hydrogen gas over palladium on carbon in

ethanol/6 N aqueous hydrochloric acid gives the amine 6-Scheme 1, which is treated with a carboxylic acid (such as N-Cbz-L-phenylalanine, N-CBz-L-norleucine, N-CBz-L-cyclohexylalanine or 4-imidazoleacetic acid), a peptide coupling reagent (such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride), 1-hydroxybenzotriazole and diisopropylethylamine in DMF to give 7-Scheme 1. When R^2 is $(CH_2)_4NHBoc$, R^3 is methyl and R^4 is isobutyl, treatment of 7-Scheme 1 with trifluoroacetic acid in methylene chloride provides 8-Scheme 1.

Scheme 2

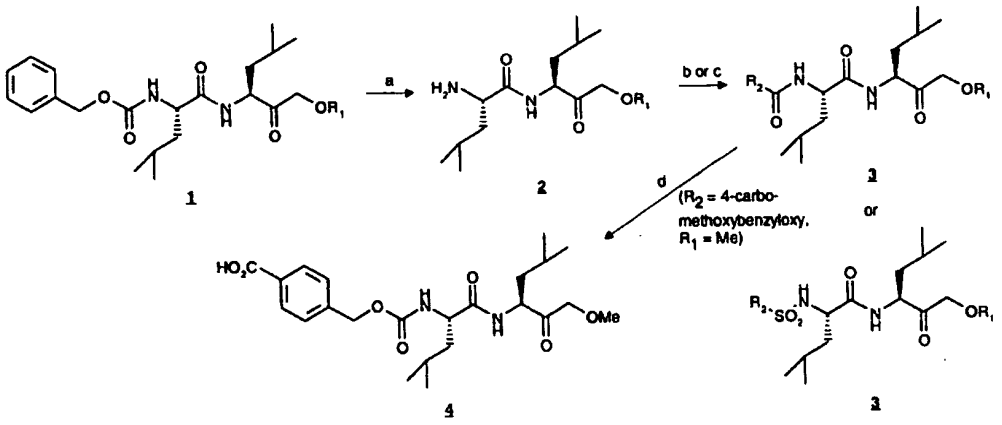


1 2 3

a) $Rh_2(OAc)_4$, R^3OH; (b) TFA, CH_2Cl_2

Compounds of the formula I wherin X = O and R^3 = methyl, ethyl, *n*-propyl, *n*-butyl, or 3-methyl-*n*-butyl are prepared by methods analagous to those described in Scheme 2. Alkoxy methyl ketones such as 2-Scheme 2 are prepared from diazoketone 2-Scheme 1 by treatment with rhodium acetate in an alcoholic solvent (such as methanol, ethanol, 1-propanol, 1-butanol, or 3-methyl-1-butanol). When R^1 is N-Cbz-L-leucine, R^2 is $(CH_2)_2CO_2t$-Bu and R^3 is ethyl, treatment of 2-Scheme 2 with trifluoroacetic acid in methylene chloride provides 3-Scheme 2.

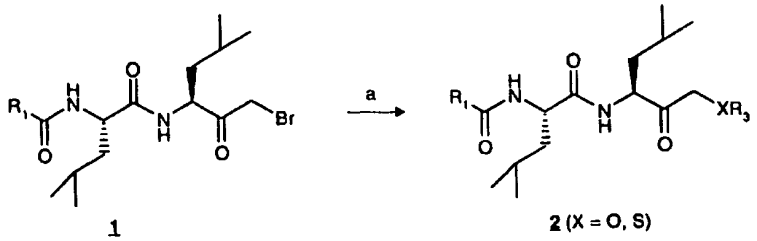
Scheme 3



a) H_2, Pd/C, EtOH, 6N hydrochloric acid; b) R^2COCl or R^2SO_2Cl, NMM, DMF; c) R^2CO_2H, EDCI, 1-HOBT, DIEA, DMF; d) LiOH, MeOH, H_20

Compounds of the formula I wherin G is other than benzyloxy are prepared by methods analagous to those described in Scheme 3. A Cbz-protected alkoxy methyl ketone 1-Scheme 3 is deprotected by treatment with hydrogen and a palladium/carbon catatlyst in ethanol with 6N hydroxhloric acid to form amine 2-Scheme 3, which was acylated with an acyl chloride (such as acetyl chloride or benzoyl chloride, or phenoxyacetyl chloride) a chloroformate (such as 4-carbomethoxybenzyl chloroformate, (R)-1-phenylethyl chloroformate, (S)-1-phenylethyl chloroformate, cyclohexylmethyl chloroformate, 2-methoxybenzyl chloroformate, 4-chlorobenzyl chloroformate, 3,4-dimethylbenzyl chloroformate, cyclopentylmethyl chloroformate, 1-naphthylmethyl chloroformate or 4-fluorobenzyl chloroformate), a carbamoyl chloride (such as 1,2,3,4-tetrahydroisoquinolyl chloride, as 1,2,3,4-tetrahydroquinolyl chloride or N-benzyl-N-methylcarbamoyl chloride) or sulfonyl chloride (such as 2-naphthylsulfonyl chloride) and N-methylmorpholine in DMF to provide 3-Scheme 3. When R^2 is 4-carbomethoxybenzyloxy, treatment of 3-Scheme 3 with lithium hydroxide in methanol/water provides 4-Scheme 3.

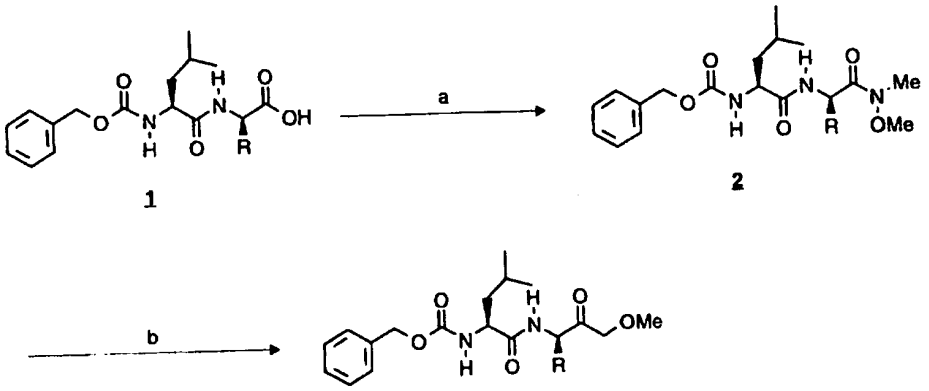
Scheme 4



a) R^3SH or ROH, KF, DMF

Compounds of the formula I wherin R^1 is Cbz or Cbz-Leucinyl, X = S, or X = O and R^3 = 1,1,1,3,3,3-hexafluoro-2-propyl, phenyl or 3,4-methylenedioxyphenyl are prepared by methods analagous to those described in Scheme 4. Bromide 1-Scheme 4 is treated with a mercaptan (such as 2-phenylethyl mercaptan, *n*-propyl mercaptan, *n*-butyl mercaptan, thiophenol or benzyl mercaptan) or an acidic alcohol (such as 1,1,1,3,3,3-hexafluoro-2-propanol, phenol or 3,4-methylenedioxyphenol) and potassium fluoride in DMF to provide 2-Scheme 4.

Scheme-5

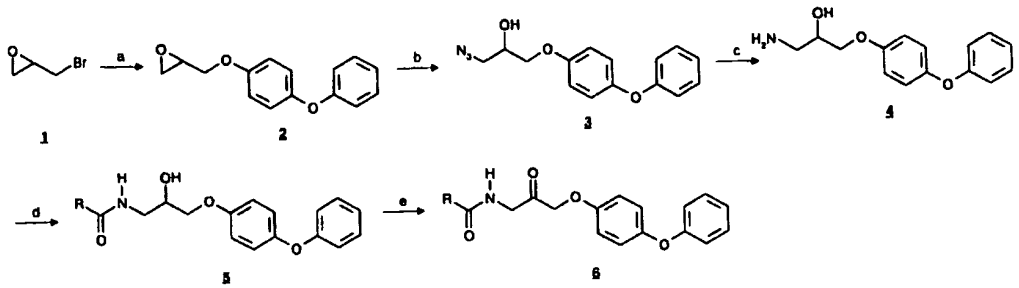


1 2 3

a) EDC•HCl, 1-HOBT, MeONHMe•HCl; b) *n*-Bu_3SnCH_2OMe, *n*-BuLi, THF, -78 °C

Compounds of the formula I wherin X = O and R^3 = methyl may be prepared by methods analagous to those described in Scheme 5. The carboxylic acid 1-Scheme 5 is converted to the N,O-dimethylhydroxamate 2-Scheme 5 by treatment with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1-hydroxybenzotriazole and N,O-dimethylhydroxylamine in methylene chloride. The amide 2-Scheme 5 is converted to 3-Scheme 5 by the addition of the organometallic reagent derived by treatment of tri-*n*-butylmethoxymethylstannane with n-butyllithium at -78°C in THF.

Scheme 6



a) 4-phenoxyphenol, DME; b) NaN_3, NH_4Cl, $MeOH/H_20$; c) H_2, Pd/C, MeOH; d) RCO_2H, EDCI, 1-HOBT, DIEA, DMF; e) Jones reagent, acetone

Compounds of the formula I wherin R^2 is H and R^3 is 4-phenoxyphenyl are prepared by methods analagous to those described in Scheme 6. Epibromohydrin (1-Scheme 6) is treated with 4-phenoxyphenol in DME to provide 2-Scheme 6, which is converted to azide 3-Scheme 6 by treatment with sodium azide and ammonium chloride in methanol water. This material is treated with hydrogen and 10% palladim on carbon in methanol to provide 4-Scheme 6 which is converted to amide 5-Scheme 6 by treatment with a carboxylic acid (such as N-Cbz-L-leucine, or N-Cbz-L-leucinyl-L-leucine), a peptide coupling reagent (such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride), 1-hydroxybenzotriazole and diisopropylethylamine in DMF. Alcohol 5-Scheme 6 is then treated with Jones reagent in acetone to provide 6-Scheme 6.

The starting materials used herein are commercially available amino acids or are prepared by routine methods well known to those of ordinary skill in the art and can be found in standard reference books, such as the COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-VI (published by Wiley-Interscience).

Coupling methods to form amide bonds herein are generally well known to the art. The methods of peptide synthesis generally set forth by Bodansky *et al.*, THE PRACTICE OF PEPTIDE SYNTHESIS, Springer-Verlag, Berlin, 1984; E. Gross and J. Meienhofer, THE PEPTIDES, Vol. 1, 1-284 (1979); and J.M. Stewart and J.D. Young, SOLID PHASE PEPTIDE SYNTHESIS, 2d Ed., Pierce Chemical Co., Rockford, Ill., 1984. are generally illustrative of the technique and are incorporated herein by reference.

Synthetic methods to prepare the compounds of this invention frequently employ protective groups to mask a reactive functionality or minimize unwanted side reactions. Such protective groups are described generally in Green, T.W, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, John Wiley & Sons, New York (1981). The term amino protecting groups generally refers to the Boc, acetyl, benzoyl, Fmoc and Cbz groups and derivatives thereof as known to the art. Methods for protection and deprotection, and replacement of an amino protecting group with another moiety are well known.

Acid addition salts of the compounds of Formula I are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. Certain of the compounds form inner salts or zwitterions which may be acceptable. Cationic salts are prepared by treating the parent compound with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation; or with an appropriate organic amine. Cations such as Li^+, Na^+, K^+, Ca^{++}, Mg^{++} and NH_4^+ are specific examples of cations present in pharmaceutically acceptable salts. Halides, sulfate, phosphate, alkanoates (such as acetate and trifluoroacetate), benzoates, and sulfonates (such as mesylate) are examples of anions present in pharmaceutically acceptable salts.

This invention also provides a pharmaceutical composition which comprises a compound according to Formula I and a pharmaceutically acceptable carrier, diluent or excipient. Accordingly, the compounds of Formula I may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of Formula I prepared as hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

The compounds of Formula I are useful for treating diseases wherein the underlying pathology is responsive to inhibition of cysteine protease activity, especially cathepsin K activity. For instance, the compounds of Formula I are useful for the treatment of conditions where undesirable bone resorption is a factor, such as osteoporosis, periodontitis, Paget's disease, hypercalcemia of malignancy, or metabolic bone disease. Cathepsin K levels have also been demonstrated to be elevated in chondroclasts of osteoarthritic synovium. Thus, selective inhibitors of cathepsin K may also have utility in treatment of diseases of excessive cartilage or matrix degradation, such as osteoarthritis or rheumatoid arthritis. Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix, and certain tumors and metastatic neoplasias may be effectively treated with the compounds of this invention.

This invention further provides a method for treating osteoporosis or inhibiting bone loss which comprises internal administration to a patient of an effective amount of a compound of Formula I, alone or in combination with other inhibitors of bone resorption, such as bisphosphonates (i.e., allendronate), hormone replacement therapy, anti-estrogens, or calcitonin. In addition, treatment with a compound of this invention and an anabolic agent, such as bone morphogenic protein, iproflavone, may be used to prevent bone loss or to increase bone mass.

For acute therapy, parenteral administration of a compound of Formula I is preferred. An intravenous infusion of the compound in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg, in a manner to maintain the concentration of drug in the plasma at a concentration effective to inhibit cathepsin K. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise amount of an inventive compound which is therapeutically effective, and route by which such compound is best administered, is readily determined by one of ordinary skill in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

The compounds of this invention may also be administered orally to the patient, in a manner such that the concentration of drug is sufficient to inhibit bone resorption or to achieve any other therapeutic indication as disclosed herein. Typically, a pharmaceutical composition containing the compound is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

Biological Assays

The compounds of this invention may be tested in one of several biological assays to determine the concentration of compound which is required to have a given pharmacological effect.

Determination of cathepsin K proteolytic catalytic activity

All assays for cathepsin K were carried out with human recombinant enzyme. Standard assay conditions for the determination of kinetic constants used a fluorogenic peptide substrate, typically Cbz-Phe-Arg-AMC, and were determined in 100 mM Na acetate at pH 5.5 containing 20 mM cysteine and 5 mM EDTA. Stock substrate solutions were prepared at concentrations of 10 or 20 mM in DMSO with 20 uM final substrate concentration in the assays. All assays contained 10% DMSO. Independent experiments found that this level of DMSO had no effect on enzyme activity or kinetic constants. All assays were conducted at ambient temperature. Product fluorescence (excitation at 360 nM; emission at 460 nM) was monitored with a Perceptive Biosystems Cytofluor II fluorescent plate reader. Product progress curves were generated over 20 to 30 minutes following formation of AMC product.

Inhibition studies

Potential inhibitors were evaluated using the progress curve method. Assays were carried out in the presence of variable concentrations of test compound. Reactions were initiated by addition of enzyme to buffered solutions of inhibitor and substrate. Data analysis was conducted according to one of two procedures depending on the appearance of the progress curves in the presence of inhibitors. For those compounds whose progress curves were linear, apparent inhibition constants ($K_{i,app}$) were calculated according to equation 1 (Brandt *et al.*, *Biochemitsry*, **1989**, *28*, 140):

$$v = V_m A / [K_a(1 + I/K_{i,\,app}) + A] \quad (1)$$

where v is the velocity of the reaction with maximal velocity V_m, A is the concentration of substrate with Michaelis constant of K_a, and I is the concentration of inhibitor.

For those compounds whose progress curves showed downward curvature characteristic of time-dependent inhibition, the data from individual sets was analyzed to give k_{obs} according to equation 2:

$$[\mathrm{AMC}] = v_{ss}\, t + (v_0 - v_{ss})\,[1 - exp\,(-k_{obs}t)] / k_{obs} \quad (2)$$

where [AMC] is the concentration of product formed over time t, v_0 is the initial reaction velocity and v_{ss} is the final steady state rate. Values for k_{obs} were then analyzed as a linear function of inhibitor concentration to generate an apparent second order rate constant (k_{obs} / inhibitor concentration or k_{obs} / [I]) describing the time-dependent inhibition. A complete discussion of this kinetic treatment has been fully described (Morrison *et al.*, *Adv. Enzymol. Relat. Areas Mol. Biol.*, **1988**, *61*, 201).

Human Osteoclast Resorption Assay

Aliquots of osteoclastoma-derived cell suspensions were removed from liquid nitrogen storage, warmed rapidly at 37°C and washed x1 in RPMI-1640 medium by centrifugation (1000 rpm, 5 min at 4°C). The medium was aspirated and replaced with murine anti-HLA-DR antibody, diluted 1:3 in RPMI-1640 medium, and incubated for 30 min on ice The cell suspension was mixed frequently.

The cells were washed x2 with cold RPMI-1640 by centrifugation (1000 rpm, 5 min at 4°C) and then transferred to a sterile 15 mL centrifuge tube. The number of mononuclear cells were enumerated in an improved Neubauer counting chamber. Sufficient magnetic beads (5 / mononuclear cell), coated with goat anti-mouse IgG, were removed from their stock bottle and placed into 5 mL of fresh medium (this washes away the toxic azide preservative). The medium was removed by immobilizing the beads on a magnet and is replaced with fresh medium.

The beads were mixed with the cells and the suspension was incubated for 30 min on ice. The suspension was mixed frequently. The bead-coated cells were immobilized on a magnet and the remaining cells (osteoclast-rich fraction) were decanted into a sterile 50 mL centrifuge tube. Fresh medium was added to the bead-coated cells to dislodge any trapped osteoclasts. This wash process was repeated x10. The bead-coated cells were discarded.

The osteoclasts were enumerated in a counting chamber, using a large-bore disposable plastic pasteur pipette to charge the chamber with the sample. The cells were pelleted by centrifugation and the density of osteoclasts adjusted to $1.5x10^4$/mL in EMEM medium, supplemented with 10% fetal calf serum and 1.7g/litre of sodium bicarbonate. 3 mL aliquots of the cell suspension (per treatment) were decanted into 15 mL centrifuge tubes. These cells were pelleted by centrifugation. To each tube 3 mL of the appropriate treatment was added (diluted to 50 uM in the EMEM medium). Also included were appropriate vehicle controls, a positive control (87MEM1 diluted to 100 ug/mL) and an isotype control (IgG2a diluted to 100 ug/mL). The tubes were incubate at 37°C for 30 min.

0.5 mL aliquots of the cells were seeded onto sterile dentine slices in a 48-well plate and incubated at 37°C for 2 h. Each treatment was screened in quadruplicate. The slices were washed in six changes of warm PBS (10 mL / well in a 6-well plate) and then placed into fresh treatment or control and incubated at 37°C for 48 h. The slices were then washed in phosphate buffered saline and fixed in 2% glutaraldehyde (in 0.2M sodium cacodylate) for 5 min., following which they were washed in water and incubated in buffer for 5 min at 37°C. The slices were then washed in cold water and incubated in cold acetate buffer / fast red garnet for 5 min at 4°C. Excess buffer was aspirated, and the slices were air dried following a wash in water.

The TRAP positive osteoclasts were enumerated by bright-field microscopy and were then removed from the surface of the dentine by sonication. Pit volumes were determined using the Nikon/Lasertec ILM21W confocal microscope.

General

Nuclear magnetic resonance spectra were recorded at either 250 or 400 MHz using, respectively, a Bruker AM 250 or Bruker AC 400 spectrometer. $CDCl_3$ is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, and CD_3OD is tetradeuteriomethanol. Chemical shifts are reported in parts per million (d) downfield from the internal standard tetramethylsilane. Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. Continuous wave infrared (IR) spectra were recorded on a Perkin-Elmer 683 infrared spectrometer, and Fourier transform infrared (FTIR) spectra were recorded on a Nicolet Impact 400 D infrared spectrometer. IR and FTIR spectra were recorded in transmission mode, and band positions are reported in inverse wavenumbers (cm^{-1}). Mass spectra were taken on either VG 70 FE, PE Syx API III, or VG ZAB H, or Micromass platform API-only instruments, using fast atom bombardment (FAB) or electrospray (ES) ionization techniques. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius.

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel.

Where indicated, certain of the materials were purchased from the Aldrich Chemical Co., Milwaukee, Wisconsin, Chemical Dynamics Corp., South Plainfield, New Jersey, and Advanced Chemtech, Louisville, Kentucky.

Examples

In the following synthetic examples, temperature is in degrees Centigrade (°C). Unless otherwise indicated, all of the starting materials were obtained from commercial sources. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. These Examples are given to illustrate the invention, not to limit its scope. Reference is made to the claims for what is reserved to the inventors hereunder.

Example 1

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1,1,1,3,3,3-hexafluoro-2-propoxy)-5-methyl-2-hexanone

a) (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-bromo-5-methyl-2-hexanone

1-methyl-3-nitro-1-nitrosoguanidine (5.9 g) in ether (200 mL) is cooled to 0°C. 40% potassium hydroxide is added slowly and the diazomethane is allowed to collect in the ether solution for 30 minutes at 0°C.

Cbz-L-leucinyl-L-leucine (4.0 gm., 10.6 mmol) is stirred in tetrahydrofuran at -40°C. N-methyl morpholine (1.07 g, 10.6 mmol, 1.16 mL) and isobutyl chloroformate (1.45 g, 10.6 mmol, 1.38 mL) are added. The mixture is stirred at -40°C for 15 minutes and then filtered into a cold flask to remove precipitated salts. To the filtered solution is added an excess of the previously prepared diazomethane solution and the mixture is allowed to stand at 0°C for 16 h. An excess of 30% HBr in acetic acid is added at 0°C and the solution is then washed successively with 1.0N citric acid, saturated aqueous sodium bicarbonate (carefully), and brine. The solution is dried over sodium sulfate, filtered, and evaporated to give the title compound as a clear solid (4.10 g). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.34 (5H, m), 6.51 (1H, d), 5.15 (1H, d), 5.10 (2H, s), 4.78 (1H, m), 4.20 (1H, m), 4.04 (2H, dd), 1.63 (6H, m), 0.93 (12H, m).

b) (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1,1,1,3,3,3-hexafluoro-2-propoxy)-5-methyl-2-hexanone

1,1,1,3,3,3 hexafluoroisopropanol (0.444 g, 2.6 mmol) was stirred in dimethylformamide at room temperature. Potassium fluoride (0.192 g, 4.0 mmol) was added and allowed to stir for 10 minutes. The compound of Example 1(a) (1.0 g, 2.6 mmol) was added and the mixture was allowed to stir overnight at room temperature. The solution was diluted with diethyl ether and washed with water. The organic layer was dried over magnesium sulfate, filtered, and evaporated to a residue which was chromatographed (silica gel, 40% ethyl acetate in hexane) to give the title compound as a white powder (0.452 g). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.24 (5H, m), 6.72 (1H, d), 5.38 (1H, d), 4.98 (2H, s), 4.61 (1H, m), 4.48 (2H, dd), 4.27 (1H, m), 4.13 (1H, m), 1.57 (6H, m), 0.80 (12H, m).

Example 2

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-1-(1,1,1,3,3,3-hexafluoro-2-propoxy)-5-methyl-2-hexanone

a) (3S)-3-L-leucinylamino-1-(1,1,1,3,3,3-hexafluoro-2-propoxy)-5-methyl-2-hexanone hydrochloride salt

The compound of Example 1(b) (0.347 g, 0.6 mmol) was dissolved in ethanol with 10% palladium on carbon (0.035 g). 6.0N hydrochloric acid (0.43 mL) was added and hydrogen gas was bubbled through the solution for 1 hour and maintained under positive hydrogen pressure overnight. The mixture was filtered and solvents evaporated to give a residue (0.317 g) which was used without further purification.

b) (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-1-(1,1,1,3,3,3-hexafluoro-2-propoxy)-5-methyl-2-hexanone

The compound of Example 2(a) (0.317 g, 0.7 mmol), Cbz-L-leucine (0.189 g, 0.7 mmol), BOP reagent (0.315 g, 0.7 mmol), and triethylamine (0.144 g, 1.4 mmol, 0.2 mL)

were stirred in dichloromethane at room temperature for 16 hours. The solution was washed with water, then brine. The organic extracts were dried over magnesium sulfate, filtered, and evaporated to give a residue which was chromatographed (silica gel, 25% ethyl acetate in hexane) to give the title compound as a white solid (0.202 g). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.26 (5H, m), 6.71 (1H,d), 6.27 (1H, d), 5.14 (1H, d), 5.06 (2H, s), 4.59 (1H, m), 4.52 (2H, dd), 4.33 (1H, m), 4.04 (1H, m), 1.53 (9H, m), 0.82 (18H, m).

Example 3

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-phenoxy-2-hexanone

Phenol (0.138 gm., 1.5 mmol) and sodium hydride (0.036 gm., 1.5 mmol) were stirred in dimethylformamide at -20°C under an argon atmosphere for 15 minutes. The compound of Example 1(a) (0.664 g, 1.5 mmol) was added and stirred for 30 minutes. The reaction mixture was warmed to room temperature and stirred for 2 hours. The mixture was neutralized with 0.3M potassium bisulfate and the solvent removed in vacuo. The residue obtained was partitioned between ethyl acetate and water and the organic extracts were washed with brine. The solution was dried over magnesium sulfate, filtered, and evaporated to give a residue which was chromatographed (silica gel, 25% ethyl acetate in hexane) to give the title compound as a white solid (0.48 g). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.26 (7H, m), 6.92 (1H, t), 6.80 (2H, d), 6.42 (1H, d), 5.13 (1H, d), 4.98 (2H, s), 4.91 (1H, m), 4.60 (2H, d), 4.12 (1H, m), 1.58 (4H, m), 1.39 (2H, m), 0.84 (12H, m).

Example 4

Preparation of (3S)-3-[(N-benzyloxycarbonyl)- L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone

a) (3S)-3-[(N-benzyloxycarbonyl)- L-leucinyl]amino-5-methyl-1-phenylglyoxylyl-2-hexanone

The compound of Example 1(a) (1.3 g, 2.9 mmol) and benzoylformic acid (0.515 g, 3.5 mmol) were stirred in dimethylformamide (10 mL) and treated with potassium fluoride (0.25 g, 4.4 mmol). The mixture was stirred for 16 hours at room temperature and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate, filtered, and evaporated to give a residue which was chromatographed (silica gel, 25% ethyl acetate in hexane) to give the title compound as a white solid (1.04 g).

b) (3S)-3-[(N-benzyloxycarbonyl)- L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone

The compound of Example 4(a) (1.02 g, 1.9 mmol) was stirred vigorously in a mixture of tetrahydrofuran (100 mL) and 1.0M potassium bicarbonate (100 mL) at room

temperature for 18 hours. The layers were seperated and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered, and evaporated to give the title compound as a white solid (0.768 g). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.21 (5H, m), 7.01 (1H, d), 5.60 (1H, d), 4.95 (2H, s), 4.56 (1H, m), 4.22 (2H, s), 4.18 (1H, m), 1.56 (6H, m), 0.78 (12H, m).

Example 5

Preparation of (3S)-3-[(N-benzyloxycarbonyl)- L-leucinyllamino-1-ethoxy-5-methyl-2-hexanone

The compound of Example 4(b) (0.38 gm., 1.0 mmol), silver oxide (0.449 g, 2.0 mmol), and ethyl iodide (0.755 g, 5.0 mmol, 0.39 mL) were stirred in refluxing dichloromethane in the dark under argon for 16 hours. The solvent was evaporated and the residue obtained was chromatographed (silica gel, 20% ethyl acetate in hexane) to give the title compound as a white solid (0.183 g). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.24 (5H, m), 6.49 (1H, d), 5.22 (1H, d), 5.01 (2H, s), 4.77 (1H, m), 4.13 (1H, m), 4.09 (2H, dd), 3.48 (2H, m), 1.52 (6H, m), 1.17 (3H,t), 0.83 (12H, m).

Example 6

Preparation of (3S)-3-[(N-benzyloxycarbonyl)- L-leucinyllamino-1-benzoyloxy-5-methyl-2-hexanone

Followong the procedure of Example 5, except substituting benzyl iodide for ethyl iodide, the title compound was prepared as a whte solid (0.174 g). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.24 (5H, m), 6.60(1H, d), 5.23 (1H, d), 5.01 (2H, s), 4.79 (1H, m), 4.51 (2H, d), 4.08 (3H, m), 1.53 (6H, m), 0.82 (12H, m).

Example 7

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(2-phenylethylthio)-5-methyl-2-hexanone

The compound of Example 1(a) (70 mg, 0.153 mmol) was treated with potassium fluoride (9 mg, 0.155 mmol), then 2-phenylethyl mercaptan (23 mg, 0.168 mmol) in DMF (4 ml) and was stirred overnight at RT. The reaction mixture was diluted with water (4 ml), then extracted with EtOAc (20 ml). The combined organic extracts were partitioned between water (3 x 20 ml), brine (20 ml), then dried over magnesium sulfate, filtered, concentrated *in vacuo*, and chromatographed (silica gel, 30% EtOAc/hexanes) to give the title compound as a white solid (45 mg, 58%). MS(ES) $M+H^+ = 513.5$, $M+Na^+ = 535.5$, $2M+Na^+ = 1047.8$.

Example 8

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(1-propylthio)-2-hexanone

Following the procedure of Example 7, except substituting *n*-propyl mercaptan for 2-phenylethyl mercaptan, the title compound was prepared. MS(ES) $M+H^+ = 451.5$, $M+Na^+ = 473.5$, $2M+Na^+ = 923.7$.

Example 9

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1-butylthio)-5-methyl-2-hexanone

Following the procedure of Example 7, except substituting *n*-butyl mercaptan for 2-phenylethyl mercaptan, the title compound was prepared. MS(ES) $M+H^+ = 513.5$, $M+Na^+ = 535.5$, $2M+Na^+ = 1047.8$.

Example 10

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(phenylthio)-5-methyl-2-hexanone

Following the procedure of Example 7, except substituting thiophenol for 2-phenylethyl mercaptan, the title compound was prepared. MS(ES) $M+H^+ = 485.5$, $M+Na^+ = 507.5$, $2M+Na^+ = 991.7$.

Example 11

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(benzylthio)-5-methyl-2-hexanone

Following the procedure of Example 7, except substituting benzyl mercaptan for 2-phenylethyl mercaptan, the title compound was prepared. MS(ES) $M+H^+ = 499.5$, $M+Na^+ = 521.5$, $2M+Na^+ = 1019.8$.

Example 12

Preparation of (3S)-3-[(N-benzyloxycarbonyl)- L-leucinyl-L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone

a) (3S)-3-[(N-Benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-1-bromo-5-methyl-2-hexanone

Followong the procedure of Example 1(a), except substituting N-benzyloxycarbonyl-L-leucinyl-L-leucinyl-L-leucine for N-benzyloxycarbonyl-L-leucinyl-L-leucine, the title compound was prepared as a glassy solid which was used without further purification.

b) (3S)-3-[(N-benzyloxycarbonyl)- L-leucinyl-L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone

Followong the procedure of Example 4(a)-4(b), except substituting (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-1-bromo-5-methyl-2-hexanone for (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-bromo-5-methyl-2-hexanone in step (a), the title compound was prepared as a white solid (1.41 g). ^1H NMR (400 MHz, $CDCl_3$) d (5H, m), 6.90 (1H, d), 6.57 (1H, d), 5.30 (1H, d), 5.01 (2H, d), 4.55 (1H, m), 4.33 (1H, m), 4.24 (2H, d), 4.08 (1H, m), 3.06 (1H, m), 1.55 (9H, m), 0.81 (18H, m).

Example 13

Preparation of (3S)-3-[(N-benzyloxycarbonyl)- L-leucinyl-L-leucinyl]amino-1-phenoxy-5-methyl-2-hexanone

Followong the procedure of Example 3, except substituting (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-1-bromo-5-methyl-2-hexanone for (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-bromo-5-methyl-2-hexanone, the title compound was prepared as a white solid (0.257 g). ^1H NMR (400 MHz, $CDCl_3$) d 7.26 (7H, m), 6.95 (1H, t), 6.88 (2H, d), 6.60 (1H, d), 6.39 (1H, d), 5.04 (2H, s), 4.89 (1H, m), 4.62 (2H, d), 4.38 (1H, m), 4.07 (1H, m), 1.59 (6H, m), 1.42 (4H, m), 0.85 (18H, m).

Example 14

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone

Following the procedure of Example 5, except substituting methyl iodide for ethyl iodide, the title compound was prepared. MS(ES) $M+H^+ = 407.5$, $M+Na^+ = 429.5$.

Example 15

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(3,4-methylenedioxyphenoxy)-5-methyl-2-hexanone

Following the procedure of Example 1(b), except substituting sesamol for 1,1,1,3,3,3-hexafluoro-2-propanol, the title compound was prepared. MS(ES) $M+H^+ = 513$, $2M+H^+ = 1025$.

Example 16

Preparation of (3S)-3-[(N-Acetyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone

a) (3S)-3-(L-leucinyl)amino-1-ethoxy-5-methyl-2-hexanone

The compound of Example 5 (250 mg, 0.60 mmol) was dissolved in EtOH (40 ml) and 6 N aqueous hydrochloric acid (0.6 ml) then 10% palladium on carbon (60 mg) was added and the reaction was stirred under a balloon of hydrogen gas for 3h. The reaction mixture was filtered and the filtrate was diluted with toluene (2 x 100 ml) and was concentrated in vacuo to remove residual water to produce a white foam which was used in the next reaction without further purification.

b) (3S)-3-[(N-Acetyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone

The compound of Example 16(a) (44 mg, 0.136 mmol) was dissolved in methylene chloride (5 ml). Acetyl chloride (11 mg, 0.15 mmol) was added, followed by triethylamine (90 mg, 0.9 mmol) and the reaction was stirred at RT for 2h. The reaction mixture was diluted with water (20 ml), then extracted with EtOAc (50 ml). The combined organic extracts were dried over magnesium sulfate, filtered, concentrated *in vacuo*, and chromatographed (silica gel, 80% EtOAc/hexanes) to give the title compound as a white solid (19 mg, 43%). MS(ES) $M+H^+ = 329$, $2M+H^+ = 657$, $2M + NH_4^+ = 674$.

Example 17

Preparation of (3S)-3-[(N-Benzoyl)-L-leucinyllamino-1-ethoxy-5-methyl-2-hexanone

Following the procedure of Example 16(b), except substituting benzoyl chloride for acetyl chloride, the title compound was prepared. MS(ES) $M+H^+ = 391$, $M+NH_4^+ = 408$.

Example 18

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-phenylalanyllamino-1-ethoxy-5-methyl-2-hexanone

a) (3S)-3-(N-benzyloxycarbonyl)amino-1-bromo-5-methyl-2-hexanone

Following the procedure of Example 1(a), except substituting N-benzyloxycarbonyl-L-leucine for N-benzyloxycarbonyl-L-leucinyl-L-leucine, the title compojnd was prepared.

b) (3S)-3-(N-benzyloxycarbonyl)amino-1-hydroxy-5-methyl-2-hexanone

Following the procedure of Example 4(a)-4(b), except substituting for (3S)-3-(N-benzyloxycarbonyl)amino-1-bromo-5-methyl-2-hexanone for (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-bromo-5-methyl-2-hexanone in step (a), the title compound was prepared.

c) (3S)-3-(N-benzyloxycarbonyl)amino-1-ethoxy-5-methyl-2-hexanone

Following the procedure of Example 5, except substituting (3S)-3-(N-benzyloxycarbonyl)amino-1-hydroxy-5-methyl-2-hexanone for (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone, the title compound was prepared.

d) (3S)-3-amino-1-ethoxy-5-methyl-2-hexanone

Following the procedure of Example 16(a), except substituting (3S)-3-(N-benzyloxycarbonyl)amino-1-ethoxy-5-methyl-2-hexanone for (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone, the title compound was prepared.

e) (3S)-3-[(N-benzyloxycarbonyl)-L-phenylalanyl]amino-1-ethoxy-5-methyl-2-hexanone

The compound of Example 18(d) (50 mg, 0.23 mmol) was dissolved in DMF (1.5 ml), then N-benzyloxycarbonyl-L-phenylalanine (75 mg, 0.25 mmol), EDCI (51 mg, 0.27 mmol), HOBT (37 mg, 0.27 mmol), and DIEA (80 mg, 0.6 mmol) were added and the reaction mixtrue was stirred overnight. The reaction mixture was diluted with water (20 ml), then extracted with ethyl acetate (50 ml). The combined organic extracts were dried over magnesium sulfate, filtered, concentrated *in vacuo*, and chromatographed (silica gel,

30% EtOAc/hexanes) to give the title compound as an oil (15 mg, 14%). MS(ES) $M+H^+$ = 455.5, $2M+Na^+$ = 477, $2M + Na^+$ = 931.7.

Example 19

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-norleucinyllamino-1-ethoxy-5-methyl-2-hexanone

Following the procedure of Example 18(e), except substituting N-benzyloxycarbonyl)-L-norleucine for N-benzyloxycarbonyl-L-phenylalanine, the title compound was prepared. MS(ES) $M+H^+$ = 421, $M+Na^+$ = 443.

Example 20

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyllamino-1-(1-propoxy)-5-methyl-2-hexanone

(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-diazo-5-methyl-2-hexanone (150 mg, 0.37 mmol) was dissolved in 1-propanol (2.5 ml), then rhodium acetate (2 mg) was added and the raction was stirred at RT for 2h. The reaction mixture was chromatographed (silica gel, 20% EtOAc/hexanes) to yield the title compound as a white solid (59 mg, 37%). MS(ES) $M+H^+$ = 435, $M+ NH_4^+$ = 452, $2M+H^+$ = 869.6.

Example 21

Preparation of (3S)-3-[(N-phenoxycarbonyl)-L-leucinyllamino-1-ethoxy-5-methyl-2-hexanone

Following the procedure of Example 16(b), except substituting phenoxyacetyl chloride for acetyl chloride, the title compound was prepared. MS(ES) $M+H^+$ = 421, $M+Na^+$ = 443.

Example 22

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-cyclohexylalanyllamino-1-ethoxy-5-methyl-2-hexanone

Following the procedure of Example 18(e), except substituting N-benzyloxycarbonyl)-L-cyclohexylalanine for N-benzyloxycarbonyl-L-phenylalanine, the title compound was prepared. MS(ES) $M+H^+$ = 461, $M+ NH_4^+$ = 478.

Example 23

Preparation of (3S)-3-[(N-Benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(3-methylbutoxy)-2-hexanone

Following the procedure of Example 20, except substituting 3-methylbutanol for 1-propanol, the title compound was prepared. MS(ES) $M+H^+ = 463.6$, $M+Na^+ = 485.5$.

Example 24

Preparation of (3S)-3-[(N-Benzyloxycarbonyl)-L-leucinyl]amino-1-(1-butoxy)-5-methyl-2-hexanone

Following the procedure of Example 20, except substituting 1-butanol for 1-propanol, the title compound was prepared. MS(ES) $M+H^+ = 449$, $M+Na^+ = 471$.

Example 25

Preparation of (3S)-7-[(benzyloxycarbonyl)amino]-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1-propoxy)-2-heptanone

a) (3S)-3,7-bis-(benzyloxycarbonyl)amino-1-diazo-2-heptanone

Following the procedure of Example 1(a), except substituting N-benzyloxycarbonyl-L-(N^{ε}-benzyloxycarbonyl)-lysine for N-benzyloxycarbonyl-L-leucinyl-L-leucine, the title compound was prepared.

b) (3S)-3,7-bis-(benzyloxycarbonyl)amino-1-(1-propoxy)-2-heptanone

Following the procedure of Example 20, except substituting (3S)-3,7-bis-(benzyloxycarbonyl)amino-1-diazo-2-heptanone for (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-diazo-5-methyl-2-hexanone, the title compound was prepared.

c) (3S)-3-amino-7-(benzyloxycarbonyl)amino-1-(1-propoxy)-2-heptanone

Following the procedure of Example 16(a), except substituting (3S)-3,7-bis-(benzyloxycarbonyl)amino-1-(1-propoxy)-2-heptanone for (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone, the title compound was prepared.

d) (3S)-7-[(benzyloxycarbonyl)amino]-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1-propoxy)-2-heptanone

Following the procedure of Example 18(e), except substituting (3S)-3-amino-7-(benzyloxycarbonyl)amino-1-(1-propoxy)-2-heptanone for (3S)-3-amino-1-ethoxy-5-methyl-2-hexanone and N-benzyloxycarbonyl-L-leucine for N-benzyloxycarbonyl-L-

phenylalanine, the title compound was prepared. MS(ES) $M+H^+ = 570.4$, $M+HCO_2^- = 614.4$.

Example 26

Preparation of (3S)-3-[[N-(4-carbomethoxy)benzyloxycarbonyl]-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone

Following the procedure of Example 16(b), except substituting 4-carbomethoxybenzoyl chloride for acetyl chloride, the title compound was prepared. MS(ES) $M+H^+ = 479.5$, $M+Na^+ = 501$, $2M+Na^+ = 979.7$.

Example 27

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-7-[(9-fluorenylmethoxycarbonyl)amino]-2-heptanone

a) (3S)-3-(N-benzyloxycarbonyl)amino-1-diazo-7-(9-fluorenylmethoxycarbonyl)amino-2-heptanone

Following the procedure of Example 1(a), except substituting N-benzyloxycarbonyl-[N^e-(9-fluorenylmethoxycarbonyl)]-L-lysine for N-benzyloxycarbonyl-L-leucinyl-L-leucine, the title compound was prepared.

b) (3S)-3-(N-benzyloxycarbonyl)amino-1-ethoxy-7-(9-fluorenylmethoxycarbonyl)amino-2-heptanone

Following the procedure of Example 20, except substituting (3S)-3-(N-benzyloxycarbonyl)amino-1-diazo-7-(9-fluorenylmethoxycarbonyl)amino-2-heptanone for (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-diazo-5-methyl-2-hexanone and ethanol for 1-propanol, the title compound was prepared.

c) (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-7-[(9-fluorenylmethoxycarbonyl)amino]-2-heptanone

Following the procedure of Example 25(c)-25(d), except substituting (3S)-3-(N-benzyloxycarbonyl)amino-1-ethoxy-7-(9-fluorenylmethoxycarbonyl)amino-2-heptanone for (3S)-3,7-bis-(benzyloxycarbonyl)amino-1-(1-propoxy)-2-heptanone in step (c), the title compound was prepared. MS(ES) $M+H^+ = 658$.

Example 28

Preparation of (4S)-*tert*-butyl 4-[(N-benzyloxycarbonyl)-L-leucinyl]amino-6-ethoxy-5-oxohexanoate

Following the procedure of Example 27(a)-27(c), except substituting N-(benzyloxycarbonyl)-L-glutamic acid-g-*tert*-butyl ester for N-benzyloxycarbonyl-[N^{ε}-(9-fluorenylmethoxycarbonyl)]-L-lysine in step (a), the title compound was prepared. MS(ES) $M+H^+ = 493.5$, $M+Na^+ = 515.4$, $2M+Na^+ = 1007.7$.

Example 29

Preparation of (4S)-4-[(N-benzyloxycarbonyl)-L-leucinyl]amino-6-ethoxy-5-oxohexanoic acid

The compound of Example 28 (30 mg, 0.06 mmol) was dissolved in methylene chloride (1 ml), then trifluoroacetic acid (1 ml) was added and the reaction was stirred at RT for 1h. The solution was concentrated *in vacuo*, then chromatographed (silica gel, 3% MeOH/methylene chloride, 1% AcOH) to give the title compound as a white solid (4.8 mg, 18%). MS(ES) $M+H^+ = 437.5$, $M+Na^+ = 459.4$, $2M+Na^+ = 895.5$.

Example 30

Preparation of (3S)-3-[[N-(4-carbomethoxy)benzyloxycarbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone

Following the procedure of Example 16(a)-16(b), except substituting (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone for (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone in step (a), and (3S)-3-(L-leucinyl)amino-1-methoxy-5-methyl-2-hexanone for (3S)-3-(L-leucinyl)amino-1-ethoxy-5-methyl-2-hexanone and 4-carbomethoxybenzoyl chloride for acetyl chloride in step (b), the title compound was prepared. MS(ES) $M+H^+ = 465$, $M+Na^+ = 487$, $2M+Na^+ = 951$.

Example 31

Preparation of (1'R, 3S)-1-methoxy-5-methyl-3-[[N-(1'-phenylethoxy)carbonyll-L-leucinyl]amino-2-hexanone

Following the procedure of Example 30, except substituting (R)-1-phenylethyl chloroformate for 4-carbomethoxybenzoyl chloride, the title compound was prepared. MS(ES) $M+H^+ = 421$, $M+Na^+ = 443$, $2M+Na^+ = 863$.

Example 32

Preparation of (3S)-3-[[N-(4-carboxybenzyloxy)carbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone

The compound of Example 30 (550 mg, 1.19 mmol) was dissolved in MeOH (18 ml), then aqueous LiOH hydrate (0.25 g, 6 mmol) in water (2ml) was added, and the reaction was stirred overnight. The reaction mixture was diluted with water (5 ml), acidified with AcOH (2 ml), then extracted with EtOAc (20 ml). The combined organic extracts were concentrated *in vacuo*, then chromatographed (silica gel, 35% EtOAc/hexanes with 1% AcOH) to give the title compound as a white solid (216 mg, 40%). MS(ES) $M+H^+$ = 451, $M+Na^+$ = 472.9, $2M+Na^+$ = 923.

Example 33

Preparation of (3S)-1-ethoxy-3-[[N-(4-imidazolyl)acetyl]-L-leucinyl]amino-5-methyl-2-hexanone

Following the procedure of Example 18(e), except substituting (3S)-3-(L-leucinyl)amino-1-methoxy-5-methyl-2-hexanone for (3S)-3-amino-1-ethoxy-5-methyl-2-hexanone and 4-imidazole acetic acid for N-benzyloxycarbonyl-L-phenylalanine, the title compound was prepared. MS(ES) $M+H^+$ = 381, $M+Na^+$ = 403, $2M+Na^+$ = 783.

Example 34

Preparation of (1'S, 3S)-1-methoxy-5-methyl-3-[[-(1'-phenylethoxy)carbonyl]-L-leucinyl]amino-2-hexanone

Following the procedure of Example 30, except substituting (S)-1-phenylethyl chloroformate for 4-carbomethoxybenzoyl chloride, the title compound was prepared. MS(ES) $M+H^+$ = 421, $M+Na^+$ = 443.

Example 35

Preparation of (3S)-1-ethoxy-5-methyl-3-[N-(2-naphthylsulfonyl)-L-leucinyl]amino-2-hexanone

Following the procedure of Example 30 except substituting 2-naphthylsulfonyl chloride for 4-carbomethoxybenzoyl chloride, the title compound was prepared. MS(ES) $M+H^+$ = 463, $M+Na^+$ = 484.9, $2M+Na^+$ = 947.

Example 36

Preparation of (3S)-1-ethoxy-5-methyl-3-[N-[2-(1,2,3,4-tetrahydroisoquinolyl)carbonyl]-L-leucinyl]amino-2-hexanone

Following the procedure of Example 30, except substituting 1,2,3,4-tetrahydroisoquinolylcarbonyl chloride 4-carbomethoxybenzoyl chloride, the title compound was prepared. MS(ES) $M+H^+ = 432$, $M+Na^+ = 454$, $2M+Na^+ = 885$.

Example 37

Preparation of (3S)-1-ethoxy-5-methyl-3-[N-[1-(1,2,3,4-tetrahydroquinolyl)carbonyl]-L-leucinyl]amino-2-hexanone

Following the procedure of Example 30, except substituting 1,2,3,4-tetrahydroquinolylcarbonyl chloride 4-carbomethoxybenzoyl chloride, the title compound was prepared. MS(ES) $M+H^+ = 432$, $M+Na^+ = 454$, $2M+Na^+ = 885.5$.

Example 38

Preparation of (3S)-3-[[N-(N-benzyl-N-methylamino)carbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone

Following the procedure of Example 30, except substituting N-benzyl-N-methylcarbamoyl chloride for 4-carbomethoxybenzoyl chloride, the title compound was prepared. MS(ES) $M+H^+ = 420$, $M+Na^+ = 442$, $2M+Na^+ = 861.5$.

Example 39

Preparation of (3S)-3-[(N-cyclohexylmethoxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone

Following the procedure of Example 30, except substituting cyclohexylmethyl chlorlformate for 4-carbomethoxybenzoyl chloride, the title compound was prepared. MS(ES) $M+H^+ = 413$, $M+Na^+ = 435$, $2M+Na^+ = 847.5$.

Example 40

Preparation of (3S)-1-methoxy-3-[[N-(2-methoxybenzyloxy)carbonyl]L-leucinyl]amino-5-methyl-2-hexanone

Following the procedure of Example 30, except substituting 2-methoxybenzyl chloroformate for 4-carbomethoxybenzoyl chloride, the title compound was prepared. MS(ES) $M+H^+ = 437$, $M+Na^+ = 460$, $2M+Na^+ = 896.5$.

Example 41

Preparation of (3S)-[[N-(4-chlorobenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone

Following the procedure of Example 30, except substituting 4-chlorobenzyl chloroformate for 4-carbomethoxybenzoyl chloride, the title compound was prepared. MS(ES) $M+H^+ = 441$, $M+Na^+ = 462.9$, $2M+Na^+ = 903$.

Example 42

Preparation of (3S)-[[N-(3,4-dimethylbenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone

Following the procedure of Example 30, except substituting 3,4-dimethylbenzyl chloroformate for 4-carbomethoxybenzoyl chloride, the title compound was prepared. MS(ES) $M+H^+ = 435$, $M+Na^+ = 457$, $2M+Na^+ = 891.5$.

Example 43

Preparation of (3S)-3-[(N-cyclopentylmethoxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone

Following the procedure of Example 30, except substituting cyclopentylmethyl chloroformate for 4-carbomethoxybenzoyl chloride, the title compound was prepared. MS(ES) $M+H^+ = 399$, $M+Na^+ = 421$, $2M+Na^+ = 819.5$.

Example 44

Preparation of (3S)-3-[[N-(2-naphthylmethoxy)carbonyl]-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone

Following the procedure of Example 30, except substituting 1-naphthylmethyl chloroformate for 4-carbomethoxybenzoyl chloride, the title compound was prepared. MS(ES) $M+H^+ = 457$, $M+Na^+ = 479$, $2M+Na^+ = 935.5$.

Example 45

Preparation of (3S)-7-amino-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-heptanone

a) (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-7-(*tert*-butoxycarbonyl)amino-1-methoxy-2-heptanone

Following the procedure of Example 18(a)-18(d), except substituting N-(benzyloxy carbonyl)-L-leucinyl-N^e-(*tert*-butoxycarbonyl)-L-lysine for N-benzyloxycarbonyl-L-leucine in step (a), (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-7-(*tert*-butoxycarbonyl)amino-1-hydroxy-2-heptanone for (3S)-3-(N-benzyloxycarbonyl)amino-1-hydroxy-5-methyl-2-hexanone and methyl iodide for ethyl iodide in step (c), (3S)-3-amino-7-(*tert*-butoxycarbonyl)amino-1-methoxy-2-heptanone for (3S)-3-amino-1-hydroxy-5-methyl-2-hexanone and N-benzyloxycarbonyl-L-leucine for N-benzyloxycarbonyl-L-phenylalanine in step (e), the title compound was prepared.

b) (3S)-3-[(N-(benzyloxy carbonyl)-L-leucinyl]amino-1-methoxy-7-amino-2-heptanone

Following the procedure of Example 29, except substituting (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-7-(*tert*-butoxycarbonyl)amino-1-methoxy-2-heptanone for (4S)-*tert*-butyl 4-[(N-benzyloxycarbonyl)-L-leucinyl]amino-6-ethoxy-5-oxohexanoate, the title compound was prepared. MS(ES) $M+H^+ = 422$.

Example 46

Preparation of (3S)-[[N-(4-fluorobenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone

Following the procedure of Example 30, except substituting 4-fluorobenzyl chloroformate for 4-carbomethoxybenzoyl chloride, the title compound was prepared. MS(ES) $M+H^+ = 425$, $M+Na^+ = 442$, $2M+H^+ = 849.6$, $2M + NH_4^+Na^+ = 866.4$.

Example 47

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-butanone

a) N-benzyloxycarbonyl-L-leucinyl-L-alanine methyl ester

Following the procedure of Example 18(e), except substituting L-alanine methyl ester for (3S)-3-amino-1-ethoxy-5-methyl-2-hexanone and N-benzyloxycarbonyl-L-leucine for N-benzyloxycarbonyl-L-phenylalanine, the title compound was prepared.

b) N-benzyloxycarbonyl-L-leucinyl-L-alanine

Following the procedure of Example 32, except substituting N-benzyloxycarbonyl-L-leucinyl-L-alanine methyl ester for (3S)-3-[[N-(4-carbomethoxy)benzyloxycarbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone, the title compound was prepared.

c) (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-bromo-2-butanone

Following the procedure of Example 1(a), except substituting N-benzyloxycarbonyl-L-leucinyl-L-alanine fo N-benzyloxycarbonyl-L-leucinyl-L-leucine, the title compound was prepared.

d) (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-hydroxy-2-butanone

Following the procedure of Example 4(a)-4(b), except substituting (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-bromo-2-butanone for (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-bromo-5-methyl-2-hexanone in step (a), the title compound was prepared.

e) (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-butanone

Following the procedure of Example 5, except substituting (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-hydroxy-2-butanone for (3S)-3-[(N-benzyloxycarbonyl)- L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone and methyl iodide for ethyl iodide, the title compound was prepared. MS(ES) $M+H^+ = 265.3$, $M+Na^+ = 287.3$.

Example 48

Preparation of (3R)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-butanone

a) N-benzyloxycarbonyl-L-leucinyl-D-alanine-*tert*-butyl ester

To a CH_2Cl_2 solution of D-alanine *tert*-butyl ester was added EDC (1.29 g, 6.76 mmol), HOBt (0.76 g, 5.63 mmol), NMM (1.85 mL, 16.89 mmol) and N-benzyloxycarbonyl-L-leucine (1.5 g, 5.63 mmol). The reaction was maintained at room temperature until all starting material was consumed as indicated by TLC analysis. The mixture was then concentrated in vacuo, diluted with ethyl acetate, washed with 1N HCl,

saturated K_2CO_3, water, brine, dried ($MgSO_4$) and concentrated to give the title compound.

b) N-benzyloxycarbonyl-L-leucinyl-D-alanine

The compound of Example 48(a) was dissolved in dry ethyl acetate and HCl gas was bubbled through it for approximately 5 minutes. This mixture was allowed to stir at room temperature until complete consumption of the starting ester was observed. The mixture was concentrated in vacuo to give the title compound (2.07 g).

c) N-benzyloxycarbonyl-L-leucinyl-D-alanine N,O-dimethylhydroxamate

To a CH_2Cl_2 solution of the compound of Example 48(b) (2.07 g) was added EDC (1.2 g) HOBT (0.83 g) and N,O-dimethyl amine. The mixture was maintained at room temperature until complete as indicated by TLC analysis. The mixture was then concentrated in vacuo, diluted with ethyl acetate, washed with 1N HCl,saturated K_2CO_3, water, brine, dried ($MgSO_4$) and concentrated to give the the title compound (1.8 g). MS(ES) $M+H^+ = 380.2$, $M+Na^+ = 402.2$.

d) (3R)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-butanone

To a -78°C solution tri-*n*-butylmethoxymethyl stannane (926 mg, 2.76 mmol) was added n-BuLi (1.07 ml of a 2.5 molar solution in hexanes, 2.68 mmol) dropwise. This solution was maintained at -78°C for approximately 20 minutes whereupon the the compound of Example 48(c) (300 mg, 0.79 mmol) in THF (10 mL) was added dropwise. This mixture was maintained at -78°C for 30 minutes whereupon it was quenched with saturated ammonium chloride and washed with ethyl acetate. The ethyl acetate layer was washed with water, brine, dried ($MgSO_4$) filtered, concentrated and the residue was chromatographed (2:1 hexanes:ethyl acetate) to give the title compound. MS(ES) $M+H^+ = 365.2$, $M+Na^+ = 387.2$.

Example 49

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(4-phenoxyphenoxy)-2-hexanone

Following the procedure of Example 1(a)-1(b), except substituting 4-phenoxyphenol of 1,1,1,3,3,3-hexafluoro-2-propanol in step (b), the title compound was prepared (152 mg). MS(ES) $M+H^+ = 561.2$, $M+Na^+ = 583.2$.

Example 50

Preparation of 1-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanone

a) 3-(4-phenoxyphenoxy)-1,2-propylene oxide

To a solution of 4-phenoxyphenol in aqueous sodium hydroxide (1.41 mL of a 0.24 molar solution; 5.9 mmol) was added epibromohydrin (1.0 g, 7.32 mmol) in DME (10 mL). The reaction mixture was maintained at room temperature for 60 hours whereupon it was diluted with ether. The ether solution was washed with saturated K_2CO_3, brine, dried ($MgSO_4$) and concentrated to give the title compound which was used directly in the following step without purification.

b) 1-azido-3-(4-phenoxyphenoxy)-2-propanol

To a solution of the compound of Example 50(a) in CH_3OH:water (9 mL of an 8:1 mixture) was added ammonium chloride (231 mg) and sodium azide (673 mg). The reaction was heated to reflux until complete by TLC analysis. Standard workup gave the title compound which was used directly in the following step without purification.

c) 1-amino-3-(4-phenoxyphenoxy)-2-propanol

To a solution of the compound of Example 50(b) (585 mg, 2.05 mmol) in CH_3OH (20 mL) was added 10 Pd/C (200 mg). This mixture was placed under an atmosphere of hydrogen and stirred until complete by TLC analysis whereupon it was filtered through a pad of celite and concentrated to give the title compound which was used directly in the next step with no further purification.

d) 1-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanol

Following the procedure of Example 18(e), except substituting 1-amino-3-(4-phenoxyphenoxy)-2-propanol for (3S)-3-amino-1-ethoxy-5-methyl-2-hexanone and N-benzyloxycarbonyl-L-leucinyl-L-leucine for N-benzyloxycarbonyl-L-phenylalanine, the title compound was prepared. MS(ES) $M+H^+ = 620.1$, $M+Na^+ = 642.1$.

e) 1-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanone

To a room temperature solution of the compound of Example 50(d) (125 mg) in acetone (10 mL) was added Jones reagent (ca. 2.0 mL). The reaction was maintained at room temperature overnight whereupon it was quenched with 2-propanol. Workup and column chromatography (1:1 hexanes:ethyl acetate) gave the title compound (94 mg). MS(ES) $M+H^+ = 618.1$, $M+Na^+ = 640.1$.

Example 51

Preparation of 1-[(N-benzyloxycarbonyl)-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanone

a) 1-[(N-benzyloxycarbonyl)-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanol

Following the procedure of Example 18(e), except substituting 1-amino-3-(4-phenoxyphenoxy)-2-propanol for (3S)-3-amino-1-ethoxy-5-methyl-2-hexanone and N-benzyloxycarbonyl-L-leucine for N-benzyloxycarbonyl-L-phenylalanine, the title compound was prepared. MS(ES) $M+H^+ = 507.1$, $M+Na^+ = 529.0$.

b) Following the procedure of Example 50(e), except substituting 1-[(N-benzyloxycarbonyl)-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanol for 1-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanol, the title compound was prepared. MS(ES) $M+H^+ = 505.1$, $M+Na^+ = 527.0$.

Example 52

Preparation of (3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(4-phenylbenzyloxy)-2-hexanone

Following the procedure of Example 5, except substituting 4-phenylbenzyl bromide for ethyl iodide, the title compound was prepared. MS(CI) $M+H^+ = 559.2$, $M+Na^+ = 581.1$.

Example 53

Preparation of (3R)-7-amino-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-heptanone

a) N^e-*tert*-butoxycarbonyl-D-lysine methyl ester

N^e-*tert*-butoxycarbonyl-D-lysine (0.5g, 2.03 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (467 mg, 2.44 mmol), 1-hydroxbenzotriazole (329 mg, 2.44 mmol), HCl (4M in dioxane, 5ml, 2.03 mmol) and methanol (0.83ml, 20.3 mmol) were stirred at RT in dichloromethane until the disapperance of the acid was observed. The organic layer was washed with saturated $NaHCO_3$, water, saturatedd NaCl and dried over Na_2SO_4. The product was purified by column chromatography to provide the title compound (240 mg) of desired product. ^1H NMR (400 MHz, $CDCl_3$) d 3.70 (s, 3H), 3.50 (m, 1H), 3.05 (m, 2H), 1.50-1.70 (m, 15H). MS(ES) $M+H^+ = 261$.

b) N-benzyloxycarbonyl-L-leucinyl-N^e-*tert*-butoxycarbonyl-D-lysine methyl ester

Following the procedure of Example 48(a), except substituting N^e-*tert*-butoxycarbonyl-D-lysine methyl ester for D-alanine *tert*-butyl ester, the title compound was prepared (88%). ^1H NMR (400 MHz, $CDCl_3$) d 7.45 (s, 5H), 5.10 (s, 2H), 4.55 (m, 2H), 3.70 (s,3H), 3.05 (m, 2H), 1.50-1.70 (m, 18H), 1.09 (d, 6H). MS(ES) $M+H^+ = 508$.

c) N-benzyloxycarbonyl-L-leucinyl-N^e-*tert*-butoxycarbonyl-D-lysine

Following the procedure of Example 32, except substituting N-benzyloxycarbonyl-L-leucinyl-N^{e}-*tert*-butoxycarbonyl-D-lysine methyl ester for (3S)-3-[[N-(4-carbomethoxy)benzyloxycarbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone, the title compound was prepared (98%). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.45 (s, 5H), 5.10 (s, 2H), 4.55 (m, 2H), 3.05 (m, 2H), 1.50-1.70 (m, 18H), 1.09 (d, 6H). MS(ES) M+H^{+} = 494.

d) (3R)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-7-[(*tert*-butoxycarbonyl)amino]-1-(1-propoxy)-2-heptanone

Following the procedure of Example 48(c)-48(d), except substituting N-benzyloxycarbonyl-L-leucinyl-N^{e}-*tert*-butoxycarbonyl-D-lysine for N-benzyloxycarbonyl-L-leucinyl-D-alanine is step (c), the title compound was prepared (56%). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.45 (s, 5H), 6.80 (d, 1H), 5.10 (s, 2H), 4.75 (m, 2H), 4.15 (m, 1H), 4.19 (d, 2H), 3.40 (s, 3H), 3.05 (m, 2H), 1.50-1.70 (m, 18H), 1.09 (d, 6H). MS(ES) M+H^{+} = 522.

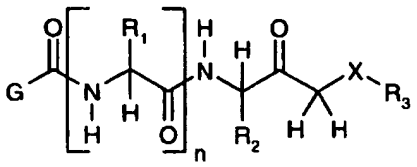
e) (3R)-7-amino-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-heptanone

Following the procedure of Example 29, except substituting (3R)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-7-[(*tert*-butoxycarbonyl)amino]-1-(1-propoxy)-2-heptanone for (4S)-*tert*-butyl 4-[(N-benzyloxycarbonyl)-L-leucinyl]amino-6-ethoxy-5-oxohexanoate, the title compound was prepared (100%). ^{1}H NMR (400 MHz, $CDCl_3$) d 8.0 (m, 3H), 7.45 (m, 5H), 5.10 (m, 2H), 4.60-4.10 (m, 4H), 3.40 (m, 3H), 3.05 (m, 2H), 1.50-1.70 (m, 9H), 0.9 (d, 6H). MS(ES) M+H^{+} = 422.

The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described herein above, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

We claim:

1. A compound according to Formula I:



I

G = $ArCHR^4O$, C_{1-4}alkyl, CH_2OAr, Ar, OCH_2C_{3-6}cycloalkyl, CH_2-imidazole, $ArSO_2$, NR^5CH_2Ar, NCH_2Ar, NAr, where the ortho position of Ar may be connected to the nitrogen by a 2 or 3 carbon chain to form a 6-membered ring;

R^1 = C_{4-6}alkyl, CH_2Ar, CH_2-C_{3-6}cycloalkyl;
with the proviso that when R^1 = isobutyl, the stereochemistry at the adjacent center is of the (S)-configuration;

R^2 = H, methyl, C_2-C_3alkyl optionally substituted by CO_2R^6 or NHR^7, isobutyl;
with the provisos that:
(a) when R^2 = isobutyl, the stereochemistry at the adjacent center must be of the (S)-configuration;
(b) when R^2 = H, methyl, R^1 cannot be CH_2Ph;

R^3 = H, C_{1-5}alkyl optionally substituted with 1-6 halogens such that no halogens are attached to the carbon adjacent to X; $(CH_2)_mAr$;

R^4 = H, C_{1-4}alkyl;

R^5 = C_{1-4}alkyl;

R^6 = H, C_{1-4}alkyl;

R^7 = H, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl;

R^8 = H, C_{1-4}alkyl;

Ar = phenyl, naphthyl
optionally substituted with 1-4 substituents selected from the group consisting of: halogen; C_{1-4}alkyl; C_{1-4}alkoxy, where optionally two adjacent C_{1-4}alkoxy substituents are combined to form a methylenedioxy ring system; CO_2R^8; phenyl; and phenoxy;

n = 0, 1;

m = 0-2;

X = O, S
with the proviso that when X = S, R^3 cannot be methyl

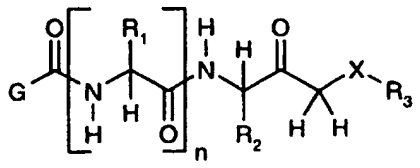
or a pharmaceutically acceptable salt thereof.

2. A compound selected from the group consisting of:

(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1,1,1,3,3,3-hexafluoro-2-propoxy)-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-1-(1,1,1,3,3,3-hexafluoro-2-propoxy)-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-phenoxy-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-1-benzyloxy-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(2-phenylethylthio)-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(1-propylthio)-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1-butylthio)-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-phenylthio-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-benzylthio-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-5-methyl-1-phenoxy-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(3,4-methylenedioxyphenoxy)-2-hexanone;
(3S)-3-[(N-acetyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzoyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-phenylalanyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-norleucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(1-propoxy)-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[(N-phenoxyacetyl)-L-leucinyl]amino-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-cyclohexylalanyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(3-methyl-1-butoxy)-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1-butoxy)-5-methyl-2-hexanone;
(3S)-7-[(benzyloxycarbonyl)amino]-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-2-heptanone;
(3S)-3-[[N-(4-carbomethoxy)benzyloxycarbonyl]-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-7-[(9-fluorenylmethoxycarbonyl)amino]-2-heptanone;
(4S)-*tert*-butyl 4-[(N-benzyloxycarbonyl)-L-leucinyl]amino-6-ethoxy-5-oxohexanoate;
(4S)-4-[(N-benzyloxycarbonyl)-L-leucinyl]amino-6-ethoxy-5-oxohexanoic acid

(3S)-3-[[N-(4-carbomethoxy)benzyloxycarbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone;
(1'R, 3S)-1-methoxy-5-methyl-3-[[N-(1'-phenylethoxy)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-3-[[N-(4-carboxybenzyloxy)carbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone;
(3S)-1-ethoxy-3-[[N-(4-imidazolyl)acetyl]-L-leucinyl]amino-5-methyl-2-hexanone;
(1'S, 3S)-1-methoxy-5-methyl-3-[[N-(1'-phenylethoxy)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[N-(2-naphthylsulfonyl)-L-leucinyl]amino-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[N-[2-(1,2,3,4-tetrahydroisoquinolyl)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[N-[1-(1,2,3,4-tetrahydroquinolyl)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-3-[[N-(N-benzyl-N-methylamino)carbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone;
(3S)-3-[(N-cyclohexylmethoxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-1-methoxy-3-[[N-(2-methoxybenzyloxy)carbonyl]L-leucinyl]amino-5-methyl-2-hexanone;
(3S)-[[N-(4-chlorobenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-[[N-(3,4-dimethylbenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[(N-cyclopentylmethoxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[[N-(2-naphthylmethoxy)carbonyl]-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-7-amino-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-heptanone;
(3S)-[[N-(4-fluorobenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-butanone;
(3R)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-butanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(4-phenoxyphenoxy)-2-hexanone;
1-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanone;
1-[(N-benzyloxycarbonyl)-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(4-phenylbenzyloxy)-2-hexanone; and
(3R)-7-amino-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-heptanone.

3. A pharmaceutical composition comprising a compound according to Formula I:



I

G = $ArCHR^4O$, C_{1-4}alkyl, CH_2OAr, Ar, OCH_2C_{3-6}cycloalkyl, CH_2-imidazole, $ArSO_2$, NR^5CH_2Ar, NCH_2Ar, NAr, where the ortho position of Ar may be connected to the nitrogen by a 2 or 3 carbon chain to form a 6-membered ring;

R^1 = C_{4-6}alkyl, CH_2Ar, CH_2-C_{3-6}cycloalkyl;

with the proviso that when R^1 = isobutyl, the stereochemistry at the adjacent center is of the (S)-configuration;

R^2 = H, methyl, C_2-C_3alkyl optionally substituted by CO_2R^6 or NHR^7, isobutyl;

with the provisos that:

(a) when R^2 = isobutyl, the stereochemistry at the adjacent center must be of the (S)-configuration;

(b) when R^2 = H, methyl, R^1 cannot be CH_2Ph;

R^3 = H, C_{1-5}alkyl optionally substituted with 1-6 halogens such that no halogens are attached to the carbon adjacent to X; $(CH_2)_mAr$;

R^4 = H, C_{1-4}alkyl;

R^5 = C_{1-4}alkyl;

R^6 = H, C_{1-4}alkyl;

R^7 = H, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl;

R^8 = H, C_{1-4}alkyl;

Ar = phenyl, naphthyl

optionally substituted with 1-4 substituents selected from the group consisting of: halogen; C_{1-4}alkyl; C_{1-4}alkoxy, where optionally two adjacent C_{1-4}alkoxy substituents are combined to form a methylenedioxy ring system; CO_2R^8; phenyl; and phenoxy;

n = 0, 1;

m = 0-2;

X = O, S

with the proviso that when X = S, R^3 cannot be methyl

and a pharmaceutically effective carrier, diluent or excipient.

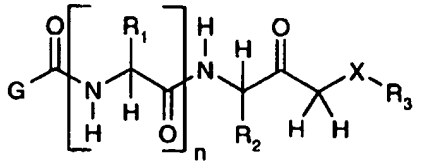
4. A pharmaceutical composition according to claim 3 wherein said compound is selected from the group consisting of:

(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1,1,1,3,3,3-hexafluoro-2-propoxy)-5-methyl-2-hexanone;

(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-1-(1,1,1,3,3,3-hexafluoro-2-propoxy)-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-phenoxy-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-1-benzyloxy-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(2-phenylethylthio)-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(1-propylthio)-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1-butylthio)-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-phenylthio-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-benzylthio-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-5-methyl-1-phenoxy-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(3,4-methylenedioxyphenoxy)-2-hexanone;
(3S)-3-[(N-acetyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzoyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-phenylalanyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-norleucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(1-propoxy)-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[(N-phenoxyacetyl)-L-leucinyl]amino-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-cyclohexylalanyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(3-methyl-1-butoxy)-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1-butoxy)-5-methyl-2-hexanone;
(3S)-7-[(benzyloxycarbonyl)amino]-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-2-heptanone;
(3S)-3-[[N-(4-carbomethoxy)benzyloxycarbonyl]-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-7-[(9-fluorenylmethoxycarbonyl)amino]-2-heptanone;
(4S)-*tert*-butyl 4-[(N-benzyloxycarbonyl)-L-leucinyl]amino-6-ethoxy-5-oxohexanoate;
(4S)-4-[(N-benzyloxycarbonyl)-L-leucinyl]amino-6-ethoxy-5-oxohexanoic acid
(3S)-3-[[N-(4-carbomethoxy)benzyloxycarbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone;
(1'R, 3S)-1-methoxy-5-methyl-3-[[N-(1'-phenylethoxy)carbonyl]-L-leucinyl]amino-2-hexanone;

(3S)-3-[[N-(4-carboxybenzyloxy)carbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone;
(3S)-1-ethoxy-3-[[N-(4-imidazolyl)acetyl]-L-leucinyl]amino-5-methyl-2-hexanone;
(1'S, 3S)-1-methoxy-5-methyl-3-[[N-(1'-phenylethoxy)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[N-(2-naphthylsulfonyl)-L-leucinyl]amino-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[N-[2-(1,2,3,4-tetrahydroisoquinolyl)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[N-[1-(1,2,3,4-tetrahydroquinolyl)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-3-[[N-(N-benzyl-N-methylamino)carbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone;
(3S)-3-[(N-cyclohexylmethoxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-1-methoxy-3-[[N-(2-methoxybenzyloxy)carbonyl]L-leucinyl]amino-5-methyl-2-hexanone;
(3S)-[[N-(4-chlorobenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-[[N-(3,4-dimethylbenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[(N-cyclopentylmethoxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[[N-(2-naphthylmethoxy)carbonyl]-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-7-amino-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-heptanone;
(3S)-[[N-(4-fluorobenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-butanone;
(3R)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-butanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(4-phenoxyphenoxy)-2-hexanone;
1-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanone;
1-[(N-benzyloxycarbonyl)-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(4-phenylbenzyloxy)-2-hexanone; and
(3R)-7-amino-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-heptanone.

5. A method of inhibiting a cysteine protease comprising administering to a patient in need thereof an effective amount of a compound according to Formula I:



I

G = $ArCHR^4O$, C_{1-4}alkyl, CH_2OAr, Ar, OCH_2C_{3-6}cycloalkyl, CH_2-imidazole, $ArSO_2$, NR^5CH_2Ar, NCH_2Ar, NAr, where the ortho position of Ar may be connected to the nitrogen by a 2 or 3 carbon chain to form a 6-membered ring;

R^1 = C_{4-6}alkyl, CH_2Ar, CH_2-C_{3-6}cycloalkyl;

with the proviso that when R^1 = isobutyl, the stereochemistry at the adjacent center is of the (S)-configuration;

R^2 = H, methyl, C_2-C_3alkyl optionally substituted by CO_2R^6 or NHR^7, isobutyl;

with the provisos that:

(a) when R^2 = isobutyl, the stereochemistry at the adjacent center must be of the (S)-configuration;

(b) when R^2 = H, methyl, R^1 cannot be CH_2Ph;

R^3 = H, C_{1-5}alkyl optionally substituted with 1-6 halogens such that no halogens are attached to the carbon adjacent to X; $(CH_2)_mAr$;

R^4 = H, C_{1-4}alkyl;

R^5 = C_{1-4}alkyl;

R^6 = H, C_{1-4}alkyl;

R^7 = H, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl;

R^8 = H, C_{1-4}alkyl;

Ar = phenyl, naphthyl

optionally substituted with 1-4 substituents selected from the group consisting of: halogen; C_{1-4}alkyl; C_{1-4}alkoxy, where optionally two adjacent C_{1-4}alkoxy substituents are combined to form a methylenedioxy ring system; CO_2R^8; phenyl; and phenoxy;

n = 0, 1;

m = 0-2;

X = O, S

with the proviso that when X = S, R^3 cannot be methyl.

6. A method according to claim 5 wherein said compound is selected from the group consisting of:

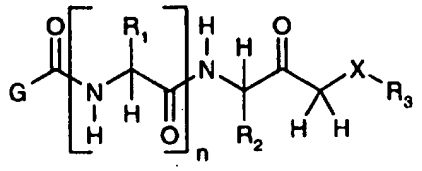
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1,1,1,3,3,3-hexafluoro-2-propoxy)-5-methyl-2-hexanone;

(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-1-(1,1,1,3,3,3-hexafluoro-2-propoxy)-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-phenoxy-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-1-benzyloxy-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(2-phenylethylthio)-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(1-propylthio)-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1-butylthio)-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-phenylthio-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-benzylthio-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-5-methyl-1-phenoxy-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(3,4-methylenedioxyphenoxy)-2-hexanone;
(3S)-3-[(N-acetyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzoyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-phenylalanyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-norleucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(1-propoxy)-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[(N-phenoxyacetyl)-L-leucinyl]amino-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-cyclohexylalanyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(3-methyl-1-butoxy)-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1-butoxy)-5-methyl-2-hexanone;
(3S)-7-[(benzyloxycarbonyl)amino]-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-2-heptanone;
(3S)-3-[[N-(4-carbomethoxy)benzyloxycarbonyl]-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-7-[(9-fluorenylmethoxycarbonyl)amino]-2-heptanone;
(4S)-*tert*-butyl 4-[(N-benzyloxycarbonyl)-L-leucinyl]amino-6-ethoxy-5-oxohexanoate;
(4S)-4-[(N-benzyloxycarbonyl)-L-leucinyl]amino-6-ethoxy-5-oxohexanoic acid
(3S)-3-[[N-(4-carbomethoxy)benzyloxycarbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone;
(1'R, 3S)-1-methoxy-5-methyl-3-[[N-(1'-phenylethoxy)carbonyl]-L-leucinyl]amino-2-hexanone;

(3S)-3-[[N-(4-carboxybenzyloxy)carbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone;
(3S)-1-ethoxy-3-[[N-(4-imidazolyl)acetyl]-L-leucinyl]amino-5-methyl-2-hexanone;
(1'S, 3S)-1-methoxy-5-methyl-3-[[N-(1'-phenylethoxy)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[N-(2-naphthylsulfonyl)-L-leucinyl]amino-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[N-[2-(1,2,3,4-tetrahydroisoquinolyl)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[N-[1-(1,2,3,4-tetrahydroquinolyl)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-3-[[N-(N-benzyl-N-methylamino)carbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone;
(3S)-3-[(N-cyclohexylmethoxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-1-methoxy-3-[[N-(2-methoxybenzyloxy)carbonyl]L-leucinyl]amino-5-methyl-2-hexanone;
(3S)-[[N-(4-chlorobenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-[[N-(3,4-dimethylbenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[(N-cyclopentylmethoxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[[N-(2-naphthylmethoxy)carbonyl]-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-7-amino-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-heptanone;
(3S)-[[N-(4-fluorobenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-butanone;
(3R)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-butanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(4-phenoxyphenoxy)-2-hexanone;
1-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanone;
1-[(N-benzyloxycarbonyl)-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(4-phenylbenzyloxy)-2-hexanone; and
(3R)-7-amino-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-heptanone.

7. A method according to claim 5 wherein the cysteine protease is cathepsin K.

8. A method of treating a disease characterized by bone loss comprising inhibiting said bone loss by administering to a patient in need thereof an effective amount of a compound according to Formula I:



I

G = $ArCHR^4O$, C_{1-4}alkyl, CH_2OAr, Ar, OCH_2C_{3-6}cycloalkyl, CH_2-imidazole, $ArSO_2$, NR^5CH_2Ar, NCH_2Ar, NAr, where the ortho position of Ar may be connected to the nitrogen by a 2 or 3 carbon chain to form a 6-membered ring;

R^1 = C_{4-6}alkyl, CH_2Ar, CH_2-C_{3-6}cycloalkyl;
with the proviso that when R^1 = isobutyl, the stereochemistry at the adjacent center is of the (S)-configuration;

R^2 = H, methyl, C_2-C_3alkyl optionally substituted by CO_2R^6 or NHR^7, isobutyl;
with the provisos that:
(a) when R^2 = isobutyl, the stereochemistry at the adjacent center must be of the (S)-configuration;
(b) when R^2 = H, methyl, R^1 cannot be CH_2Ph;

R^3 = H, C_{1-5}alkyl optionally substituted with 1-6 halogens such that no halogens are attached to the carbon adjacent to X; $(CH_2)_mAr$;

R^4 = H, C_{1-4}alkyl;

R^5 = C_{1-4}alkyl;

R^6 = H, C_{1-4}alkyl;

R^7 = H, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl;

R^8 = H, C_{1-4}alkyl;

Ar = phenyl, naphthyl
optionally substituted with 1-4 substituents selected from the group consisting of: halogen; C_{1-4}alkyl; C_{1-4}alkoxy, where optionally two adjacent C_{1-4}alkoxy substituents are combined to form a methylenedioxy ring system; CO_2R^8; phenyl; and phenoxy;

n = 0, 1;

m = 0-2;

X = O, S
with the proviso that when X = S, R^3 cannot be methyl.

9. A method according to claim 11 wherein said compound is compound is selected from the group consisting of:
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1,1,1,3,3,3-hexafluoro-2-propoxy)-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-1-(1,1,1,3,3,3-hexafluoro-2-propoxy)-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-phenoxy-2-hexanone;

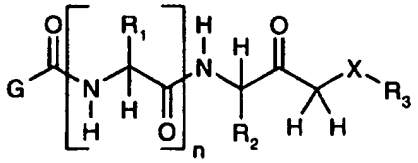
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-1-benzyloxy-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(2-phenylethylthio)-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(1-propylthio)-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1-butylthio)-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-phenylthio-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-benzylthio-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-5-methyl-1-phenoxy-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(3,4-methylenedioxyphenoxy)-2-hexanone;
(3S)-3-[(N-acetyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzoyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-phenylalanyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-norleucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(1-propoxy)-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[(N-phenoxyacetyl)-L-leucinyl]amino-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-cyclohexylalanyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(3-methyl-1-butoxy)-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1-butoxy)-5-methyl-2-hexanone;
(3S)-7-[(benzyloxycarbonyl)amino]-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-2-heptanone;
(3S)-3-[[N-(4-carbomethoxy)benzyloxycarbonyl]-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-7-[(9-fluorenylmethoxycarbonyl)amino]-2-heptanone;
(4S)-*tert*-butyl 4-[(N-benzyloxycarbonyl)-L-leucinyl]amino-6-ethoxy-5-oxohexanoate;
(4S)-4-[(N-benzyloxycarbonyl)-L-leucinyl]amino-6-ethoxy-5-oxohexanoic acid
(3S)-3-[[N-(4-carbomethoxy)benzyloxycarbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone;
(1'R, 3S)-1-methoxy-5-methyl-3-[[N-(1'-phenylethoxy)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-3-[[N-(4-carboxybenzyloxy)carbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone;
(3S)-1-ethoxy-3-[[N-(4-imidazolyl)acetyl]-L-leucinyl]amino-5-methyl-2-hexanone;

(1'S, 3S)-1-methoxy-5-methyl-3-[[N-(1'-phenylethoxy)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[N-(2-naphthylsulfonyl)-L-leucinyl]amino-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[N-[2-(1,2,3,4-tetrahydroisoquinolyl)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[N-[1-(1,2,3,4-tetrahydroquinolyl)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-3-[[N-(N-benzyl-N-methylamino)carbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone;
(3S)-3-[(N-cyclohexylmethoxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-1-methoxy-3-[[N-(2-methoxybenzyloxy)carbonyl]L-leucinyl]amino-5-methyl-2-hexanone;
(3S)-[[N-(4-chlorobenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-[[N-(3,4-dimethylbenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[(N-cyclopentylmethoxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[[N-(2-naphthylmethoxy)carbonyl]-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-7-amino-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-heptanone;
(3S)-[[N-(4-fluorobenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-butanone;
(3R)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-butanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(4-phenoxyphenoxy)-2-hexanone;
1-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanone;
1-[(N-benzyloxycarbonyl)-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(4-phenylbenzyloxy)-2-hexanone; and
(3R)-7-amino-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-heptanone.

10. A method according to claim 8 wherein said disease is osteoporosis.

11. A method according to claim 8 wherein said disease is periodontitis.

12. A method of treating a disease characterized by excessive cartilage or matrix degradation comprising inhibiting said excessive cartilage or matrix degradation by administering to a patient in need thereof an effective amount of a compound according to Formula I:



I

G = $ArCHR^4O$, C_{1-4}alkyl, CH_2OAr, Ar, OCH_2C_{3-6}cycloalkyl, CH_2-imidazole, $ArSO_2$, NR^5CH_2Ar, NCH_2Ar, NAr, where the ortho position of Ar may be connected to the nitrogen by a 2 or 3 carbon chain to form a 6-membered ring;

R^1 = C_{4-6}alkyl, CH_2Ar, CH_2-C_{3-6}cycloalkyl;

with the proviso that when R^1 = isobutyl, the stereochemistry at the adjacent center is of the (S)-configuration;

R^2 = H, methyl, C_2-C_3alkyl optionally substituted by CO_2R^6 or NHR^7, isobutyl;

with the provisos that:

(a) when R^2 = isobutyl, the stereochemistry at the adjacent center must be of the (S)-configuration;

(b) when R^2 = H, methyl, R^1 cannot be CH_2Ph;

R^3 = H, C_{1-5}alkyl optionally substituted with 1-6 halogens such that no halogens are attached to the carbon adjacent to X; $(CH_2)_mAr$;

R^4 = H, C_{1-4}alkyl;

R^5 = C_{1-4}alkyl;

R^6 = H, C_{1-4}alkyl;

R^7 = H, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl;

R^8 = H, C_{1-4}alkyl;

Ar = phenyl, naphthyl

optionally substituted with 1-4 substituents selected from the group consisting of: halogen; C_{1-4}alkyl; C_{1-4}alkoxy, where optionally two adjacent C_{1-4}alkoxy substituents are combined to form a methylenedioxy ring system; CO_2R^8; phenyl; and phenoxy;

n = 0, 1;

m = 0-2;

X = O, S

with the proviso that when X = S, R^3 cannot be methyl.

13. A method according to claim 12 wherein said compound is selected from the group consisting of:

(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1,1,1,3,3,3-hexafluoro-2-propoxy)-5-methyl-2-hexanone;

(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-1-(1,1,1,3,3,3-hexafluoro-2-propoxy)-5-methyl-2-hexanone;

(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-phenoxy-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-1-benzyloxy-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(2-phenylethylthio)-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(1-propylthio)-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1-butylthio)-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-phenylthio-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-benzylthio-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-1-hydroxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-5-methyl-1-phenoxy-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(3,4-methylenedioxyphenoxy)-2-hexanone;
(3S)-3-[(N-acetyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzoyl)-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-phenylalanyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-norleucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(1-propoxy)-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[(N-phenoxyacetyl)-L-leucinyl]amino-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-cyclohexylalanyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(3-methyl-1-butoxy)-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-(1-butoxy)-5-methyl-2-hexanone;
(3S)-7-[(benzyloxycarbonyl)amino]-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-2-heptanone;
(3S)-3-[[N-(4-carbomethoxy)benzyloxycarbonyl]-L-leucinyl]amino-1-ethoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-ethoxy-7-[(9-fluorenylmethoxycarbonyl)amino]-2-heptanone;
(4S)-*tert*-butyl 4-[(N-benzyloxycarbonyl)-L-leucinyl]amino-6-ethoxy-5-oxohexanoate;
(4S)-4-[(N-benzyloxycarbonyl)-L-leucinyl]amino-6-ethoxy-5-oxohexanoic acid
(3S)-3-[[N-(4-carbomethoxy)benzyloxycarbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone;
(1'R, 3S)-1-methoxy-5-methyl-3-[[N-(1'-phenylethoxy)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-3-[[N-(4-carboxybenzyloxy)carbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone;
(3S)-1-ethoxy-3-[[N-(4-imidazolyl)acetyl]-L-leucinyl]amino-5-methyl-2-hexanone;

(1'S, 3S)-1-methoxy-5-methyl-3-[[N-(1'-phenylethoxy)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[N-(2-naphthylsulfonyl)-L-leucinyl]amino-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[N-[2-(1,2,3,4-tetrahydroisoquinolyl)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-1-ethoxy-5-methyl-3-[N-[1-(1,2,3,4-tetrahydroquinolyl)carbonyl]-L-leucinyl]amino-2-hexanone;
(3S)-3-[[N-(N-benzyl-N-methylamino)carbonyl]-L-leucinyl]amino-5-methyl-1-methoxy-2-hexanone;
(3S)-3-[(N-cyclohexylmethoxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-1-methoxy-3-[[N-(2-methoxybenzyloxy)carbonyl]L-leucinyl]amino-5-methyl-2-hexanone;
(3S)-[[N-(4-chlorobenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-[[N-(3,4-dimethylbenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[(N-cyclopentylmethoxycarbonyl)-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[[N-(2-naphthylmethoxy)carbonyl]-L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-7-amino-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-heptanone;
(3S)-[[N-(4-fluorobenzyloxy)carbonyl]L-leucinyl]amino-1-methoxy-5-methyl-2-hexanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-butanone;
(3R)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-butanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(4-phenoxyphenoxy)-2-hexanone;
1-[(N-benzyloxycarbonyl)-L-leucinyl-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanone;
1-[(N-benzyloxycarbonyl)-L-leucinyl]amino-3-(4-phenoxyphenoxy)-2-propanone;
(3S)-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-5-methyl-1-(4-phenylbenzyloxy)-2-hexanone; and
(3R)-7-amino-3-[(N-benzyloxycarbonyl)-L-leucinyl]amino-1-methoxy-2-heptanone.

14. A method according to claim 12 wherein said disease is osteoarthritis.

15. A method according to claim 12 wherein said disease is rheumatoid arthritis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/11501

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/307, 311, 357, 390, 613, 617, 625; 546/139, 152, 329; 548/335.1; 564/123, 154, 156, 180, 181, 215, 218

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS COMPUTER SEARCH 1966-TO DATE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	EP 0 525 420 A1 (MITSUBISHI KASEI CORPORATION) 03 February 1993, see entire document, especially page 5, lines 1-50.	1-15 ------- 1-15
A	EP 0 611 756 A2 (TAKEDA CHEMICAL INDUSTRIES LTD.) 24 August 1994, see entire document.	1-15
A	EP 0 603 873 A1 (MITSUBISHI KASEI CORPORATION) 29 June 1994, see entire document.	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

17 SEPTEMBER 1997

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/11501

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07C 233/02, 233/16, 233/21, 233/22; C07D 213/30, 213/32, 215/14, 217/16; A61K 31/165, 31/415, 31/44, 31/47

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/307, 311, 357, 390, 613, 617, 625; 546/139, 152, 329; 548/335.1; 564/123, 154, 156, 180, 181, 215, 218